FORMULATION AND EVALUATION OF HYDRODYNAMICALLY BALANCED SYSTEM OF BACLOFEN.

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IN

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Submitted by

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CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND EVALUATION OF HYDRODYNAMICALLY BALANCED SYSTEM OF BACLOFEN"** was carried out by **Mathivanan**. **M** (Reg. No: 26119206), under the guidance of **Mr. D. Sakthivel M.Pharm., Ph.D., Assistant Professor** in the Department of Pharmaceutics, PGP College of Pharmaceutical Science and Research Institute, Namakkal, Affiliated to The Tamilnadu Dr. M.G.R Medical University, Chennai - 32.

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DECLARATION

I hereby declare that the matter embodied in the dissertation entitled **"FORMULATION AND EVALUATION OF HYDRODYNAMICALLY BALANCED SYSTEM OF BACLOFEN"** is a bonafide and genuine research work carried by us under the guidance of **Mr. D.SAKTHIVEL, M.Pharm., Ph.D.,** Assistant Professor, Department of Pharmaceutics, PGP College of Pharmaceutical Science & Research Institute, NH-7, Karur Main Road, Namakkal.

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ABSTRACT

Spasticity is a feature of altered skeletal muscle performance in muscle tone involving hypertonia; it is also referred to as an unusual "tightness", stiffness, or "pull" of muscles palsy and spinal. Spasticity, a condition in which certain muscles are continuously contracted, affects over 12 million worldwide. Baclofen is the largest prescribed drug for this indication, worldwide. Even though once-daily extended release GRS is available in the market, it is very expensive as it is a coated multi-layer gas generating floating tablet. The main objective is to develop once-daily sustained release gastro-retentive floating system of Baclofen in an economical way by using HPMC and natural gums. Fourteen formulations of floating matrix tablets of Baclofen (F1 – F14) were prepared by using different polymers and additives (HPMC K100M, HPMC K15M, HPMC K4M, Guar gum Xanthan gum PEO WSR301,- 303, sodium bicarbonate, Avicel PH-102, Talc, Magnesium stearate) at different concentrations by direct compression method. The formula 11 was found to be optimum and released 98.47% of Baclofen in 24hrs. . Hence, it was selected as the optimized formulation. Marketed formulation exhibited FLT of 63.67±4.01 seconds, TFT of 24 hours and released 95.07±0.41% drug in 24 hours. Finally, once-daily sustained release gastro-retentive floating tablets of Baclofen were successfully formulated in a relatively economical way when compared to the marketed formulation and found to be superior when compared to the marketed formulation.

LIST OF ABBREVIATIONS

AVICEL	Micro crystalline cellulose
BCF	Baclofen
CO_2	Carbon dioxide
FDDS	Floating drug delivery systems
FLT	Floating lag time
FT-IR spectroscopy	Fourier transform infrared spectroscopy
GRS	Gastro-retentive system
GRT	Gastric retention time
GIT	Gastrointestinal tract
HBS	Hydrodynamically balanced system
HCl	Hydrochloric acid
HPLC	High performance liquid chromatography
HPMC	Hydroxy propyl methyl cellulose
MMC	Migrating myoelectric cycle
$NaHCO_3$	Sodium bicarbonate
PEO	Poly ethylene oxide
RPM	Rotations per minute
S.D	Standard deviation
SR	Sustained release
TFT	Total floating time
USP	United States pharmacopoeia
UV	Ultra violet
VIS	Visible

CONTENTS

CHAPTER 1
INTRODUCTION

MODIFIED RELEASE ORAL DRUG DELIVERY SYSTEMS:

The oral route represents nowadays the predominant and most preferable route for drug delivery. Unlike the majority of parenteral dosage forms, it allows ease of administration by the patient and it's the natural, and therefore a highly convenient way for substances to be introduced into the human body.

Oral drug delivery systems (DDS) are mainly immediate release (conventional) drug delivery systems which are intended to disintegrate rapidly, and exhibit instant drug release. They are associated with a fast increase and decrease, and hence fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increased incidence of side effects. Administration of the DDS several times per day is therefore necessary to compensate the decrease in drug plasma concentration due to metabolism and excretion leading to poor patient compliance.

In order to overcome the drawbacks associated with conventional drug delivery systems, several technical advancements have led to the development of Modified release systems that could revolutionize method of medication and provide a number of therapeutic benefits.

Modified release systems, have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients (APIs) and patient compliance(reducing the frequency of dosing), as well as reducing the side effects[1-3].Oral modified release delivery systems are most commonly used for 1) delayed release (e.g., by using an enteric coating); 2) extended release (e.g., zero-order, first-order, biphasic release, etc.); 3) programmed release (e.g., pulsatile, triggered, etc.) and 4) site specific or timed release (e.g., for colonic delivery or gastric retention). Extended, sustained or prolonged release drug delivery systems are terms used synonymously to describe this group of controlled drug delivery devices, with predictability and reproducibility in the drug release kinetics[4]**.** Delayed release dosage forms are distinguished from the ones mentioned above as they exhibit a pronounced lag time before the drug is released. Oral extended release dosage forms offer the opportunity to provide constant or nearly constant drug plasma levels over an extended period of time following administration[5]. Two basic types of extended release dosage forms are designed to generate temporal input profile for drug delivery[6].

Matrix systems: It consists of rate controlling polymer, which is uniformly dissolved or dispersed with drug.

Reservoir system: This type of system separates drug compartment from polymer membrane that permits a diffusion barrier to yield drug flux of either zero order or first order.

Extended release DDS offer several advantages compared to conventional DDS including[7]:

i. Avoiding drug level fluctuations by maintenance of optimal therapeutic plasma and tissue concentrations over prolonged time periods, avoiding sub-therapeutic as well as toxic concentrations, thus minimizing the risk of failure of the medical treatment and undesirable side effects;

ii. Reducing the administered dose while achieving comparable effects;

iii. Reduced frequency of administration leading to improved patient compliance and subsequently improved efficacy of the therapy and cost effectiveness;

iv. Targeting or timing of the drug action. Hence, it is highly desirable to develop sustained DDS releasing the drug at predetermined rates to achieve optimal drug levels at the site of action.

On the other hand, drugs administered as sustained or extended release oral dosage form should comply with the following parameters:

i. Maintain a constant plasma level over prolonged time periods;

ii. Have a broad therapeutic window to avoid health hazard to the patient in case of undesirable burst release of the nominal dose[8].

Using current release technology, oral delivery for 24 hours is possible for many drugs but the drug should have good absorption throughout the gastrointestinal tract (GIT), preferably by passive diffusion, to ensure continuous absorption of the released drug. A major constraint in oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the GIT. Such drugs are said to have an absorption window i.e., absorbed only from specific areas of the GIT, principally due to their low Permeability or solubility in the intestinal tract, their chemical instability, the binding of

the drug to the gut contents, as well as to the degradation of the drug by the microorganisms present in the colon[9-12]. Therefore, in instances where the drug is not absorbed uniformly over the G.I tract, the rate of drug absorption may not be constant inspite of the drug delivery system delivering the drugs at a constant rate into the G.I fluids. More particularly, in instances where a drug has a clear cut absorption window (the drug is absorbed only from specific regions of the GIT like the stomach or upper parts of the small intestine), it may not be completely absorbed leading to unpredictable bioavailability and times to achieve peak plasma levels when administered in the form of a typical oral controlled drug delivery system. It is due to the relatively brief gastric emptying in humans, which normally averages 2-3 hrs through the major absorption zone. It may cause incomplete drug release from the dosage form at absorption sites leading to diminished efficacy of the administered dose. It is apparent that for a drug having such an absorption window, an effective oral controlled drug delivery system should be designed not only to deliver the drug at a controlled rate, but also to retain the drug in the stomach for a long period of time. For this drug, increased or more predictable availability would result if controlled release systems could be retained in the stomach for extended periods of time.

GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS:

Dosage forms that can be retained in the stomach for prolonged and predictable period of time are called gastro-retentive drug delivery systems (GRDDS).The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance[13]. Therefore, extended / sustained release DDS possessing gastric retention Properties may be potentially useful[14] .

Basic Gastrointestinal Tract Physiology:

To comprehend the considerations taken in the design of gastric retention dosage forms and to evaluate their performance the relevant anatomy and physiology of the G.I tract must be fully understood.

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus)(**Fig.1.1**). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions[15].

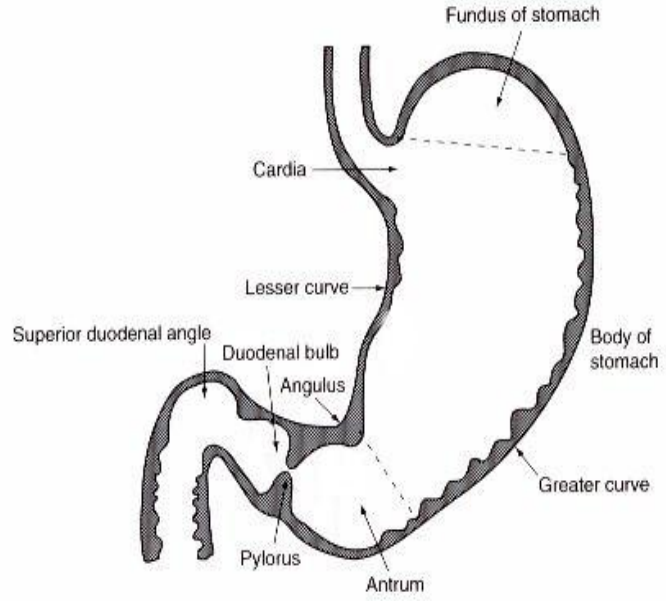


Fig 1.1: Anatomy of the stomach

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours[16]. This is called the inter-digestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington[17] (**Fig.1.2**).

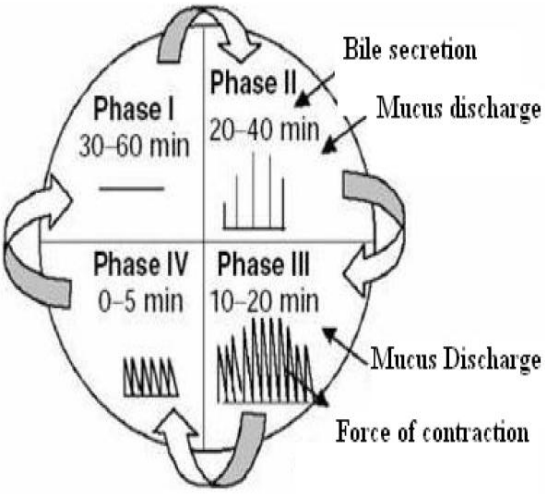


Fig 1.2: Inter-digestive myoelectric cycle (MMC)

- Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
- Phase II (pre-burst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
- Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate[18].

Requirements for Gastro-retention:

From the discussion of the physiology of the stomach, to achieve gastro-retention, the dosage form must satisfy some requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and constant grinding and churning mechanisms (phase III). It must resist premature gastric

emptying and once the purpose has been served, it should be removed from the stomach with ease.

Factors controlling gastric retention of dosage forms

The gastric retention time (GRT) of dosage forms is controlled by several factors such as:

Density of dosage form:

Dosage forms having a density lower than that of gastric fluid experience floating behavior and hence gastric retention. A density of <1.0 gm/cm^3 is required to exhibit floating property. However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium[19].

Size of dosage form:

The size of the dosage form is another factor that influences gastric retention. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be small, medium, and large units. In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeeping waves. In most cases, the larger the size of the dosage form, the greater will be the gastric retention time[20] because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine. Thus the size of the dosage form appears to be an important factor affecting gastric retention.

Food intake and nature of food:

Food intake, the nature of the food, caloric content, and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the stomach influences the GRT of the dosage form. Usually, the presence of food increases the GRT of the dosage form and increases drug absorption by allowing it to stay at the absorption site for a longer time. In a gamma scintigraphic study of a bilayer floating capsule of misoprostol[21], the mean gastric residence time was 199 ± 69 minutes; after a light breakfast, a remarkable enhancement of average GRT to 618 ± 208 minutes was observed. The above results are supported by the experiments of Whitehead et al.[22]

which show an increase in the relative heights of the floating units after meal consumption.

Effect of gender, posture and age:

A study by Mojaverian et.al.[23] found that females showed comparatively shorter mean ambulatory GRT than males, and the gastric emptying in women was slower than in men. The authors also studied the effect of posture on GRT, and found no significant difference in the mean GRT for individuals in upright, ambulatory and supine state. On the other hand, in a comparative study in humans by Gansbeke et.al.[24] the floating and non-floating systems behaved differently. In the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions, and the floating units remained away from the pylorus.

Since many factors could lead to alterations in gastric emptying process, which may seriously affect the release of a drug from its delivery system, it is therefore, desirable to develop a DDS that exhibits an extended GI residence and a drug release profile independent of patient related variables.

APPROACHES TO GASTRO- RETENTION

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems mainly include: Floating/Buoyant systems, Bio-adhesive systems, Swelling and expanding systems, High density systems(**Fig.1.3**).

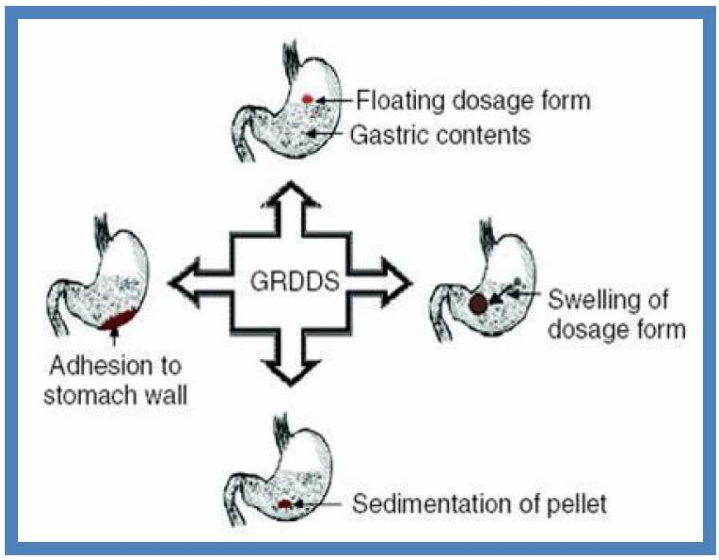


Fig 1.3: Approaches to gastro-retention

Bio/Muco-adhesive Systems:

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane.

The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio/muco-adhesive polymers.

Limitation of these systems is the gastric epithelial mucin turnover, which effects the reproducibility of these systems.

Swelling and Expanding Systems :

These are the dosage forms, which after swallowing; swell to an extent(12-18 mm in their expanded state) that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as "*plug type system*", since they exhibit the tendency to remain logged at the pyloric sphincter. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state. A balance between the extent and duration of swelling is maintained

by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.

Limitation of this system is, it requires certain period of time for swelling of these systems during which they can be emptied from the stomach.

High Density Systems:

These systems with a density of about 3g/cm^3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm^3 acts as a threshold value after which such systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc.

Limitation: These systems remain close to the pyloric splincter, which may result in gastric emptying of these systems.

Floating Drug Delivery/ Hydrodynamically balanced Systems (FDDS/ HBS):

Floating systems, first described by **Davis** in 1968[25], are low-density systems that have a density of less than 1 g/ml, to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased GRT and reduces fluctuation in plasma drug concentration. This system is shown in **Fig.1.4**.

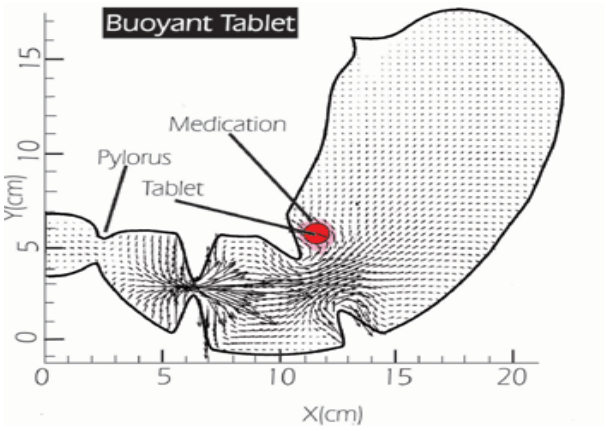


Fig 1.4: Graphic of Buoyant tablet, which is less dense than the stomach fluid and therefore remains in the fundus.

Advantages of FDDS[26]:

- **Sustained Drug Delivery:** Sustained drug absorption from oral controlled release dosage form is often limited due to short gastric retention time. However, FDDS remain in the stomach for several hours to increase their GRT. Thus, prolongation in the GRT results in sustained drug release at the absorption site.
- **Absorption or Bioavailability Enhancement:** FDDS enhances the bioavailability of active agent by, beneficially altering its absorption.
- **Site Specific Drug Delivery:** FDDS greatly improve stomach pharmacotherapy through local drug release, which leads to high drug concentrations at the gastric mucosa making it possible to treat duodenal ulcers, gastritis and oesophagitis, and reduce the risk of gastric carcinoma.
- **Carriers:** FDDS can be used as carriers for drugs such as antiviral, antifungal and antibacterial agents which are taken up only from very specific site of gastrointestinal tract (GIT). These drugs are said to have absorption window.
- **Patient Compliance:** FDDS have been recommended to improve patient compliance and convenience due to less frequent drug administration and the nature of the drug's release kinetics.
- **Fewer side effects:** FDDS show a decrease in total adverse effects with improved absolute bioavailability of the drug due to reduction of fluctuation in drug blood concentration and maximum utilization of the drug.
- **Improved plasma levels**: An increased safety margin of highly potent drugs can be achieved by formulating them as FDDS, due to better control of plasma concentration and expulsion of the floating system from the stomach after complete release *of* the drug which reduced suppression of the drug's activity by the body (i.e. counter activity) and minimized adverse activity at the colon.
- FDDS provide maintenance of systemic drug concentration within the therapeutic window, and provide site specific drug delivery. Drugs with absorption sites in the

upper small intestine, such as furosemide and riboflavin can be typically formulated using this system.

Limitations of FDDS[26]:

- The major disadvantage of floating systems is requirement of a sufficiently high level of fluids in the stomach for the drug delivery i.e. upto 400ml of gastric fluids should be present for optimum buoyancy In order to keep these tablets floating *in-vivo*, intermittent administration of water is beneficial, as the ability to float relies on the hydration state of the dosage form.

- The drugs that have solubility or stability problems in the gastric fluid and may cause irritation to gastric mucosa cannot be formulated as FDDS.

- Drugs which are well absorbed along the entire GIT and which undergo significant first pass metabolism, may not be formulated as FDDS since the slow gastric emptying may lead to reduced systemic bioavailability.

Suitable Drug Candidates for FDDS include[26]:

- Drugs acting locally in the stomach. Ex: Antacids, misoprostol and drugs used eradication of H.pylori, (the causative organism for chronic gastritis and peptic ulcer) Ex:Tetracycline.
- Drugs with a narrow window of absorption from the stomach and upper part of the GIT. Ex: Riboflavin and Levodopa.
- Drugs having stability at the acidic environment of the stomach and non-irritant to the gastric mucosa.
- Drugs that have low solubility at high pH values. Ex:Verapamil
- Drugs that are unstable in the intestine or colonic environment. Ex: Ranitidine.
- Drugs that disturb normal colonic bacteria. Ex: Amoxicillin trihydrate.

Drugs that are unsuitable for FDDS[26]:

- Drugs that have very limited acid solubility (e.g. phenytoin).
- Drugs that suffer instability in the gastric environment (e.g. erythromycin).
- Drugs intended for selective release in the colon [e.g. 5-amino salicylic acid,

corticosteroids]

1.1 Types of floating drug delivery systems (FDDS)[26]:

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:

1.1.1. Effervescent System, and
1.1.2. Non- Effervescent System.

1.1.1 Effervescent System:

These effervescent systems further classified into two types.

1.1.1.1. Gas Generating systems

1.1.1.2. Volatile Liquid Containing Systems.

1.1.1.1. Gas – Generating Systems:

These are matrix type of systems prepared with the help of hydrophilic swellable polymers such as Hydroxy propyl methylcellulose, polysaccharides and various effervescent compounds, e.g., sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in jellified hydrocolloids, which provide buoyancy to the dosage forms by lowering the density of the dosage forms. The mechanism of floating of a gas generating system is shown in **Fig.1.5.**

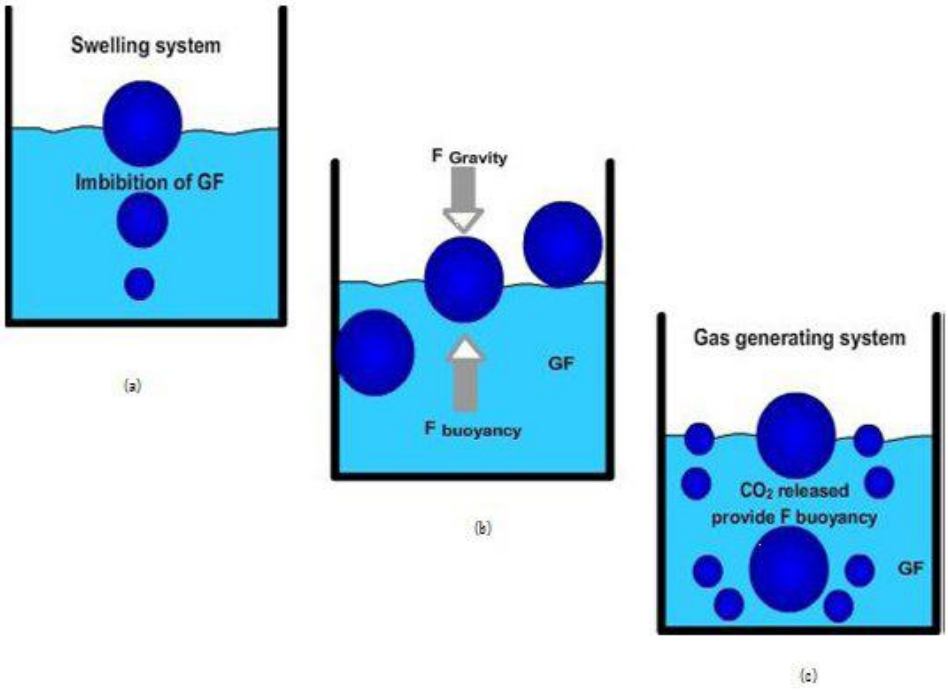


Fig1.5: Mechanism of floating systems(GF= Gastric fluid)

$$F = F_{buoyancy} - F_{gravity}$$

$$= (D_f - D_s)\, gv \text{--- (1)}$$

where, F= total vertical force, D_f = fluid density,D_s = object density, v = volume and g=acceleration due to gravity.

Types of gas generating systems include:

***1.1.1.1.1*. Intragastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS) [27]:**

The system is shown in **Fig.1.6** and formulated by intimately mixing the CO_2 generating agents, drug and the polymer within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

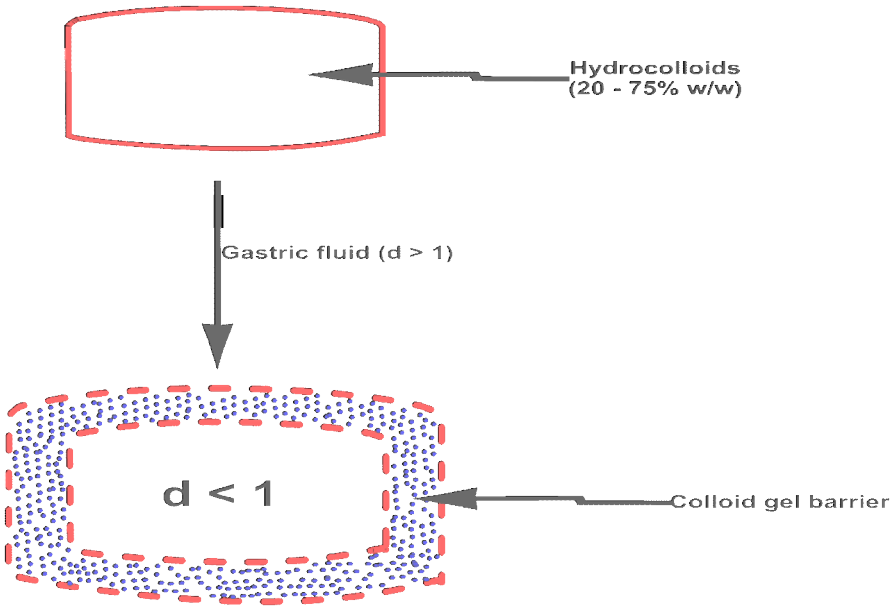


Fig 1.6: Intragastric Single Layer Buoyant Tablet.

1.1.1.1.2. Intragastric Bilayer Floating Tablets [28]:

These are compressed bi-layer tablets containing two layers(**Fig.1.7**), the gas generating mechanism in one hydrocolloid containing layer and the drug in the other layer(containing a release controlling polymer) formulated for a SR effect. After contact with acidic aqueous media, CO_2 is generated and entrapped within the gelling hydrocolloid, causing the system to float; meanwhile the drug was released in a sustained manner from the SR layer.

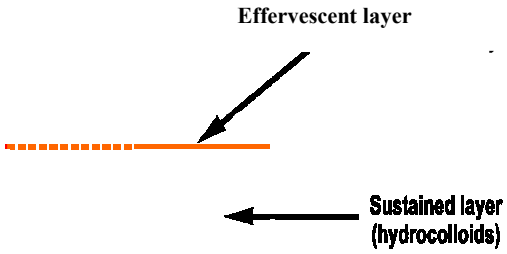


Fig 1.7: Intra Gastric Bilayer Buoyant Tablet

1.1.1.1.3. Intragastric triple layer Floating Tablets:

A floating dosage form of triple drug regimen was developed by **Yang et al.** [29] to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole, and clarithromycin) for the treatment of Helicobacter pylori–associated peptic ulcers. The design of the delivery system was based on the swellable asymmetric triple-layer tablet approach (**Fig.1.8)**. Two drugs were incorporated into the core layer of the triple-layer matrix for controlled delivery, while third drug was included in one of the outer layers for instant release. The floatation was accomplished by incorporating a gas-generating layer consisting of sodium bicarbonate: calcium carbonate (1:2 ratios) along with the polymers.

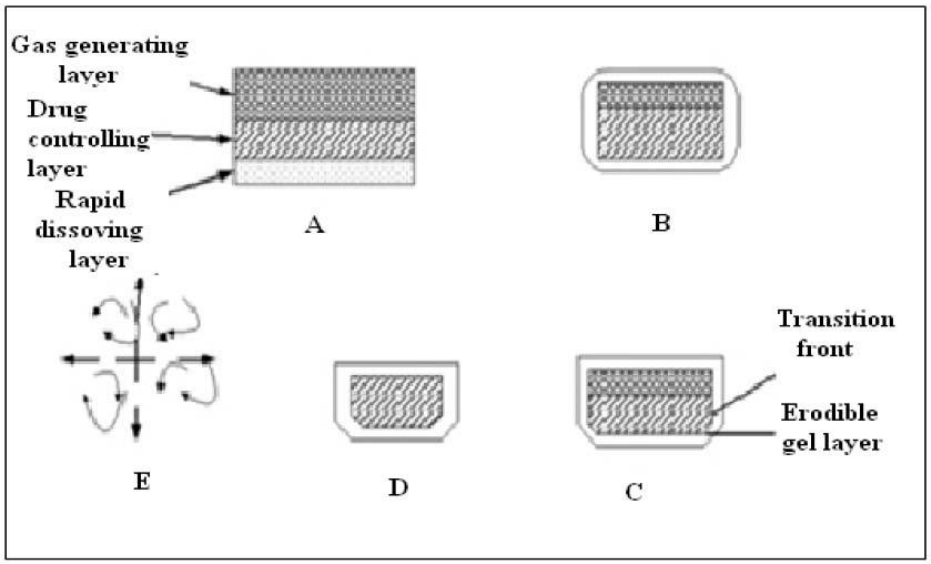


Figure1.8: Schematic presentation of working of a triple-layer system. (A) Initial configuration of triple-layer tablet. (B) On contact with the dissolution medium the bismuth layer rapidly dissolves and matrix starts swelling. (C) Tablet swells and erodes. (D) and (E) Tablet erodes completely.

1.1.1.1.4. Multiple Unit type floating pills:

This system was developed by **Ichikawa et al**.[30] The system consisted of sustained release pills as seeds surrounded by double layers **(Fig.1.9).** The inner layer was a double effervescent layer containing both $NaHCO_3$ and tartaric acid to avoid direct contact between sodium bicarbonate and tartaric acid. The outer layer was a swellable membrane layer containing mainly PVA and purified shellac. Following contact with aqueous media, it formed swollen balloon like pills, with a density much lower than 1 g/ ml, due to

the carbon dioxide generated by the neutralization reaction in the inner effervescent layers with the diffusion of water through the outer swellable membrane layer. The system was found to float completely within 10 minutes and approximately 80% remained floating over a period of 5 h irrespective of pH and viscosity of the test medium. Meanwhile, the drug was released.

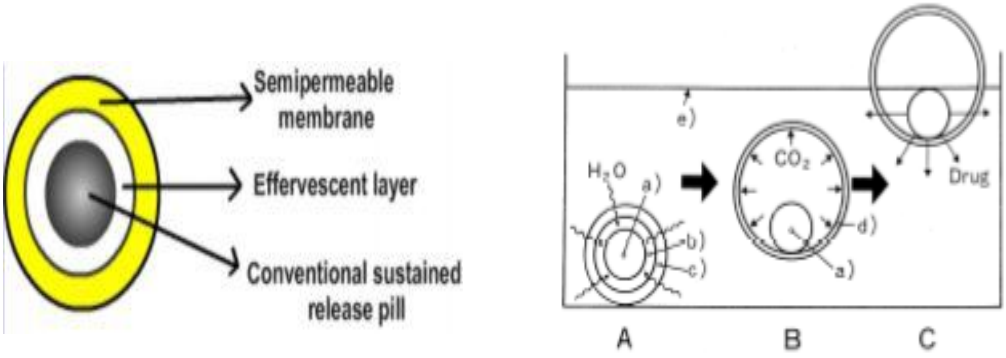


Fig 1.9: A multi-unit oral buoyant dosage system. Stages of floating mechanism: (A) penetration of water; (B) generation of CO_2 and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37^0C)

1.1.1.2. Volatile Liquid containing Systems:

- ***Intragastric Osmotically Controlled Drug Delivery System*[31,32]:**

The system comprises of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside contains gases with a boiling point < 37°C (e.g., cyclopentane, diethyl ether) incorporated in solidified or liquefied form. At physiological temperatures, the liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within

a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug release through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach. This system is shown in **Fig 1.10**.

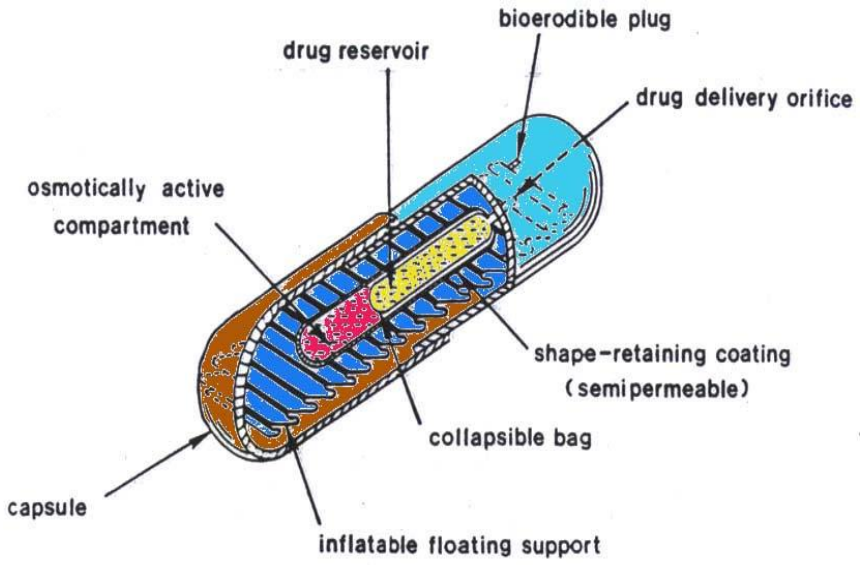


Fig1.10: Intragastric Osmotically Controlled Drug Delivery System

1.1.2 Non-Effervescent systems: [33]

The approach involved in the formulation of floating dosage forms is intimate mixing of drug with a gel forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier. The air entrapped by the swollen polymer confers buoyancy to these dosage forms. The gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier. Commonly used excipients, here are gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene.

The limitation of this approach is that floating concept in an HBS is rather passive, i.e., it mainly depends on the air captured into the dry mass inside the hydrating gelatinous surface layer. Because of this passivity, the buoyancy of an HBS largely depends on the characteristics and amount of hydrophilic polymers used.

This system can be further divided into four sub-types:

1.1.2.1 Colloidal gel barrier system:

Sheth and **Toussounian**[34] developed a HBS capsule containing a mixture of a drug and hydrocolloids. Upon contact with gastric fluids, the capsule shell dissolves and the mixture swells and forms a gelatinous barrier thereby remaining buoyant in the gastric juice for an extended period of time. Pharmaceutical products, using the same principle, containing APIs have been developed, containing L-DOPA, combined with a decarboxylase inhibitor. This system is shown in **Fig.1.11**.

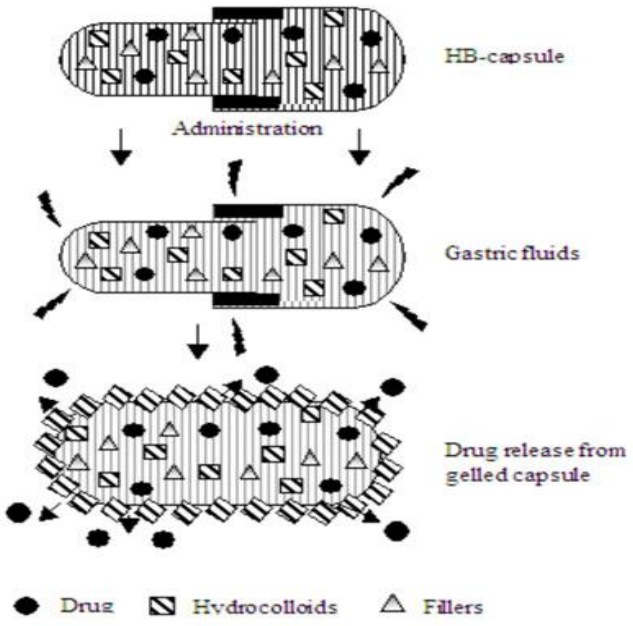


Fig 1.11: Colloidal gel barrier system

1.1.2.2 Microporous compartment system:

A multiple-unit gastro-retentive DDS which contained air compartments was developed by **Iannuccelli *et al.***[35].The units forming the system were composed of a calcium alginate core separated by an air compartment from a membrane of calcium alginate or

calcium alginate/ polyvinyl acetate (PVA). In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

1.1.2.3 Alginate Beads:

Whitehead *et al.* [36] developed multiple unit floating freeze dried calcium alginate beads of approximately 2.5 mm diameter by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system. These beads maintained a positive floating force for over 12 hrs.

1.1.2.4 Hollow Microspheres:

Hollow microspheres (micro balloons) (**Fig.1.12**), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method [37]**.** The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40^0C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The micro balloons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours in-vitro.

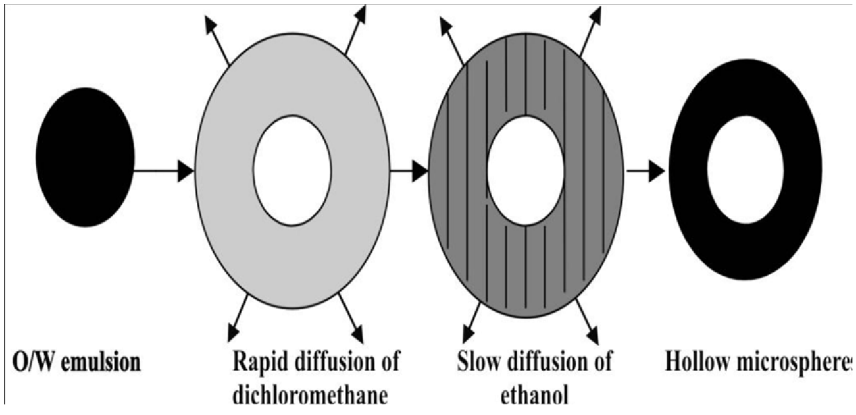


Fig 1.12: Hollow microspheres

Table1.2: Marketed Products of FDDS[26]:

S.NO.	BRAND NAME	DRUG (DOSE)	COMPANY, COUNTRY	DOSAGE FORM
1.	Modular®	Levodopa (100 mg), Benserazide (25 mg)	Roche Products, USA	Floating CR capsule
2.	Val release®	Diazepam (15 mg)	Hoffmann-Larches, USA	Floating capsule
3.	Liquid Gavison®	Al hydroxide (95 mg), Mg carbonate (358 mg)	GlaxoSmith Kline, India	Effervescent floating liquid alginate preparation
4.	Topalkan®	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid alginate preparation
5.	Conviron	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS
6.	Cifran OD®	Ciprofloxacin (500 mg, 1 gm)	Ranbaxy, India	Gas-generating floating tablet
7.	Cytotec®	Misoprostol (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule
8.	Oflin OD®	Ofloxacin (400mg)	Ranbaxy, India	Gas generating floating tablet
9.	Baclof OD	Baclofen (20 mg)	Intas Pharmaceuticals,India	Coated multi-layer gas generating floating tablet

CHAPTER 2

LITERATURE REVIEW

Past work on Baclofen sustained release drug delivery system:

Very few findings were published/ carried out on BCF sustained release drug delivery system.

- **Rishad R. Jivani et al. (2009)** [43] developed a self correcting monolithic gastro-retentive tablet of Baclofen. PEO WSR-303 was used as the polymer and sodium bicarbonate was used as the effervescent agent in the formulation. Tablets were prepared by direct compression technique. The in-vitro dissolution studies were carried out using USP XXI type II (Paddle method) Dissolution Rate Test Apparatus at 37 $\pm$ 0.5°C and 50 rpm speed. 900 mL of 0.1N HCl was used as the dissolution medium. The tablets successfully sustained the drug release upto 12 hours. The optimized formulation exhibited a floating lag time of 120 seconds and a total floating time of 12 hours. Kinetics of drug release from the tablet followed Korsmeyer – Peppas model by anamolous non-fickian diffusion.

- **Rishad R. Jivani et al. (2010)** [44] developed a novel floating *In-situ* gelling system for stomach specific drug delivery of the narrow absorption window drug Baclofen**.** Sodium alginate-based *in-situ* gelling systems were prepared by dissolving various concentrations of sodium alginate in deionized water, to which varying concentrations of drug and calcium bicarbonate were added. The in-vitro dissolution studies were carried out using USP XXI type II (Paddle method) Dissolution Rate Test Apparatus at 37 $\pm$ 0.5°C and 50 rpm speed. 500 mL of 0.1N HCl was used as the dissolution medium. The tablets successfully sustained the drug release upto 12 hours. The floating lag time and floating time of the optimized formulation were found to be 120 seconds and 12 hrs respectively. The drug release from the *in-situ* gel followed Higuchi model, which indicates a diffusion-controlled release.

- **Prema R et al. (2010)** [45] formulated sustained release matrix tablets of Baclofen for treatment of spasticity resulting from multiple sclerosis, flexor spasm and muscular rigidity. The matrix tablets were prepared by wet granulation method using HPMC K4M, K100M and xanthan gum in various concentrations. The in-vitro dissolution studies were carried out using USP XXI type II (Paddle method) Dissolution Rate Test Apparatus at 37 $\pm$ 0.5°C and 50 rpm speed. 900 mL of 0.1N HCl (pH 1.2) was used as the dissolution medium for the first 2 hrs, followed by pH 6.8 for remaining period of time. The final formulation B7 (25% HPMC K4M and K100M) extented the

release of Baclofen upto 12hrs. Model fitting analysis for the final formulation fitted in the zero order model and Korsemeyer- Peppas model. The 'n' values obtained from the Korsemeyer- Peppas equation suggested that, drug release was non-Fickian diffusion mechanism. It was concluded that sustained release matrix tablets of Baclofen containing 25% of HPMC K4M and HPMC K100M provide a better option for sustained release of drug.

- **Stephen Rathinaraj B et al. (2010)** [46] developed sustained release matrix tablets of Baclofen. The matrix tablets were prepared using using hydrophilic swellable polymers (HPMC K15M & guargum) and water insoluble polymer like ethyl cellulose by employing wet granulation method. The in-vitro release studies were performed in 0.1 N HCl for first two hours and in 7.4 pH phosphate buffer upto 12 hours. The final formulation containing 10 % guargum showed better release i.e, 80 – 90 % drug release within l0 -11 hours and successfully sustained the release of drug upto 12 hours.

- **Gande S et al. (2011)** [47] developed sustained release effervescent floating matrix tablets of Baclofen. Polymers Methocel K100M, Methocel K15M, HPMC E6-LV and effervescent agent sodium bicarbonate were used in the formulation. Tablets were prepared by wet granulation technique. The in-vitro dissolution studies were carried out using USP XXI type II (Paddle method) Dissolution Rate Test Apparatus at 37 $\pm$ 0.5°C and 50 rpm speed. 900mL of 0.1N HCl was used as the dissolution medium. The tablets successfully sustained the drug release upto 12 hours. The optimized formulation exhibited a floating lag time of 180 seconds and a total floating time of 12 hours. For all formulations, kinetics of drug release from tablet followed Higuchi's square root of time kinetic treatment heralding diffusion as predominant mechanism of drug release. There was no significant change in the selected formulations, when subjected to accelerated stability conditions over a period of three months. X-ray studies were investigated. X-ray imaging in six healthy human volunteers revealed a mean gastric retention period of 5.50±0.7 hrs for the selected formulation.

- **Upendra Kulkarni et al. (2011)** [48] fabricated bi-layer matrix tablets of Baclofen using ethylcellulose consisting of two layers such as fast releasing layer and sustaining layer. Fast releasing layer was prepared by using super disintegrant like

sodium starch glycolate and sustained release layer was prepared by using synthetic polymer like ethyl cellulose by wet granulation method. The *In vitro* release studies were performed in 0.1 N HCl for first two hr and in 7.4 pH phosphate buffer upto 24 hrs. It was observed that final formulation containing 50% ethyl cellulose successfully sustained the release of drug upto 24 hours.

CHAPTER 3

DRUG PROFILE

BACLOFEN[39-42]:

Category: Synthetic Antispastic agent or muscle Relaxant.

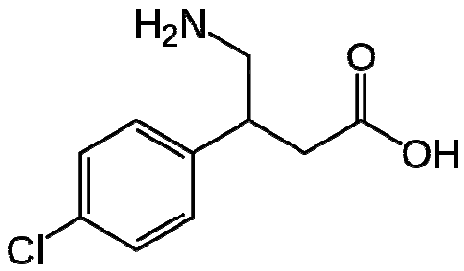
Chemical Name: 4-amino-3-(4-chlorophenyl)-butanoic acid

Molecular Formula: $C_{10}H_{12}Cl\ NO_2$

Description:

Baclofen is a white powder to off- white, virtually odorless, crystalline powder with slightly bitter taste. It has a molecular weight of 213.66. It is slightly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in acetone. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

Chemical Structure:



Dissociation Constant:pKa 3.87

Partition Co-efficient : Log P (octanol/water), 1.3

Clinical Pharmacology:

Indication: For the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity.

Mechanism of Action:

The precise mechanism of action of Baclofen is not fully known. Baclofen is capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Although Baclofen is an analog of the putative

inhibitory neurotransmitter gamma-amino-butyric acid (GABA), there is no conclusive evidence that actions on GABA systems are involved in the production of its clinical effects. In studies with animals, Baclofen has been shown to have general CNS depressant properties as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression.

Pharmacokinetics:

Absorption: Baclofen is rapidly and extensively absorbed in the upper GIT. Absorption may be dose-dependent, being reduced with increasing doses. Following a single 20 mg oral dose, the peak plasma concentration(178 ng/mL) was reached about 0.5-3 hours after administration.

Distribution: The apparent volume of distribution is 59 liters. Baclofen does not readily cross the blood-brain barrier. Plasma protein binding is approximately 30%.

Metabolism: In a study using radiolabeled Baclofen, approximately 85% of the dose was excreted unchanged in the urine and feces. About 15% of the dose was metabolized, primarily by deamination. The γ-hydroxy metabolite, 3-(p-chlorophenyl)-4-hydroxybutyric acid, is formed after deamination of Baclofen.

Excretion: About 70 to 80% of a dose is excreted in the urine mainly as unchanged drug. The remainder is excreted as unchanged drug in the feces or as metabolites in the urine and faeces. The elimination half-life of Baclofen is approximately 2.5-4 hours. Total systemic clearance is 180 mL/min and renal clearance is 103 mL/min.

Pharmacodynamics:

Baclofen is a muscle relaxant and antispastic agent. Baclofen is useful for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity. Although Baclofen is an analog of the putative inhibitory neurotransmitter gamma-aminobutyric acid (GABA), there is no conclusive evidence that actions on GABA systems are involved in the production of its clinical effects. In studies with animals, Baclofen has been shown to have general CNS depressant properties as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression. Baclofen is rapidly and extensively absorbed and eliminated. Absorption may

be dose-dependent, being reduced with increasing doses. Baclofen is excreted primarily by the kidney in unchanged form and there is relatively large intersubject variation in absorption and/or elimination.

Dosage: Oral: Severe chronic spasticity:

Adult: Initially, 5mg t.i.d for three days followed by 10mg t.i.d three days until 20mg t.i.d or desired effect is obtained.

Maximum Daily dose: 100 mg

Child: 0.75-2 mg/kg daily.May initiate with 2.5 mg 4 times daily, increased gradually every 3 days until desired effect is obtained.

Maintenance*:* 6-10 yr:30-60mg daily;2-6 yr:20-30 mg daily;12 months-2 yr:10-20 mg daily.

Elderly: Initiate with lower doses.

Contraindications: Baclofen should not be administered to patients with a history of Hypersensitivity and Active peptic ulcer disease.

Drug Interactions:

Alcohol and other CNS depressants may exacerbate the CNS effects of Baclofen and should be avoided; severe aggravation of hyperkinetic symptoms may possibly occur in patients taking lithium. There may be increased weakness if Baclofen is given to patients taking a tricyclic antidepressant and there may be an increased hypotensive effect if it is given to patients receiving antihypertensive therapy. Ibuprofen and other drugs that produce renal insufficiency may reduce Baclofen excretion leading to toxicity.

Dopaminergics: For reports of patients with Parkinson's disease taking levodopa who have had adverse effects when given Baclofen.

NSAID's: There has been a report of an elderly patient who developed Baclofen toxicity after *ibuprofen* therapy was also started. It appeared that acute renal insufficiency caused by ibuprofen had impaired Baclofen excretion.

Adverse Drug Reactions:

Adverse effects associated with Baclofen are often transient and dose-related. They may be minimised by increasing doses gradually or controlled by a reduction in dosage.

The most common adverse effects include drowsiness, nausea, dizziness, lassitude, lightheadedness, confusion, fatigue, muscular pain and weakness, and hypotension. Other adverse effects include euphoria,hallucinations, depression, headache, tinnitus, convulsions, paraesthesias, slurred speech, dry mouth, taste alterations, vomiting, diarrhoea or constipation, ataxia, nystagmus, tremors, insomnia, visual disturbances, skinrashes, pruritus, increased sweating, urinary disturbances, respiratory or cardiovascular depression, blood sugar changes, alterations in liver function values, and a paradoxical increase in spasticity. Problems with erection and ejaculation have also been reported with intrathecal Baclofen; these are usually reversible on withdrawal of therapy.

Overdosage:-

Over dosage may lead to muscular hypotonia, hypothermia, drowsiness, respiratory depression, coma, and convulsions. Stopping Baclofen abruptly may result in a withdrawal syndrome.

Treatment of Baclofen overdosage is symptomatic. Consideration should be given to the use of activated charcoal in adults who have ingested more than 100 mg, and children who have taken more than 5 mg/kg, within an hour of presentation. Alternatively, gastric lavage may be considered in adults within an hour of ingesting a life-threatening overdose. Haemodialysis should be considered in severe cases. Observation should continue for at least 6 hours after ingestion.

CHAPTER 4

OBJECTIVES

AIM AND OBJECTIVE:

Spasticity, a condition in which certain muscles are continuously contracted, affects over 12 million worldwide. Generally, spasticity is associated with common neurological disorders like multiple sclerosis, stroke, cerebral palsy and spinal cord injury. Baclofen and Tizanidine are the drugs of choice. Baclofen is the largest prescribed drug for this indication, world wide.

In the market, Baclofen is available as conventional tablets, orally disintegrating tablets and once-daily GRS tablets. The conventional and orally disintegrating tablets need to be administered 3-4 times a day (for several days) leading to poor patient compliance and there is also increased incidence of side effects with these formulations. The patient compliance can be improved and the side effects can be minimized with the once-daily formulation. Even though once-daily extended release GRS is available in the market (Baclof OD, INTAS pharmaceuticals), it is very expensive as it is a coated multi-layer gas generating floating tablet.

Rationale for Drug Selection[38]:

- Baclofen has a biological half-life of 2.5-4 hours. Hence, the conventional tablets need to be administered 3-4 times a day (for several days) leading to poor patient compliance. Therefore, Baclofen is suitable candidate for the development of once-daily formulation.
- Adverse events associated with Baclofen can be minimised when administered as once-daily formulation.
- Absorption of the Baclofen is limited to stomach or upper part of the GI tract i.e, its absorption on arrival to colon (or even before) is low or nonexistent and therefore its bioavailability is incomplete when administered as a normal sustained release formulation. The bioavailability of the drug can be increased by making the drug completely absorbed in the stomach by sustained release gastro-retentive drug delivery system considering the fact that Baclofen is stable under gastric condition.

CHAPTER 5

PLAN OF WORK

Preformulation Studies

- Determination of solubility of BCF in 0.1N HCl.
- To characterize the in-situ interactions between the drug and other excipients, if any by FT-IR examination.
- Determination of pre-compression parameters of the powder blends of various formulations.

Formulation

- To develop suitable formulae and procedure for the manufacture of BCF sustained release floating tablets in a relatively economical way.
- To formulate BCF SR floating matrix tablets using polymers HPMC K4M ,HPMC K15M, HPMC K100M, Polyethylene oxide WSR-301, Polyethylene oxide WSR-303 (synthetic polymers) and Xanthan, guar gum (natural polymers) and sodium bicarbonate as the effervescent agent by direct compression technique.

Evaluation

- To evaluate the post-compression parameters of the prepared tablets.
- In-vitro evaluation of the gastro-retentive tablets for the buoyancy and drug release characteristics.
- To analyze the rate and mechanism of release of Baclofen from the prepared floating tablets and the marketed formulation.
- Selection of the optimized formulation.
- Comparison of the optimized formulation with the marketed product.
- Determination of similarity factor.

In view of these objectives, an extensive literature search was done and the important aspects were highlighted in the chapter, “Literature Review”.

CHAPTER 6

MATERIALS AND METHODS

Table 5.1: Materials used for the formulation development

S.No.	Materials	Source
1	Baclofen	Gift sample from Natco pharma Ltd.,Hyderabad
2	HPMC K4M	Colorcon Asia Pvt Ltd.,Goa
3	HPMC K15M	Colorcon Asia Pvt Ltd.,Goa
4	HPMC K100M	Colorcon Asia Pvt Ltd.,Goa
5	Xanthan gum	Loba Chemie Pvt. Ltd., Mumbai
6	Guar gum	Loba Chemie Pvt. Ltd., Mumbai
7	PEO WSR-301	Colorcon Asia Pvt Ltd.,Goa
8	PEO WSR-303	Colorcon Asia Pvt Ltd.,Goa
9	Sodium bicarbonate	S.D. Fine chemicals Ltd., Mumbai
10	Avicel PH-102	Signet chemical corporation, Mumbai
11	Talc	S.D. Fine chemicals Ltd., Mumbai
12	Magnesium stearate	S.D. Fine chemicals Ltd., Mumbai
13	Hydrochloric acid	Loba Chemie Pvt. Ltd., Mumbai

Table 5.2: Instruments and Equipment used for the investigation

S.No.	Name of the Instrument/ Equipment	Manufacturers name
1	Electronic weighing balance	Dhona-200D
2	Micropipettes	S.D. Fine chemicals Ltd., Mumbai
3	Double beam UV-VIS spectrophotometer	Shimadzu UV-1800
4	Single beam UV-VIS Spectrophotometer	Elico SL-150
5	Rotary shaker	Remi Rotary Shaker
6	FT-IR Spectrophotometer	Perkin-Elmer, Spectrum 100 FTIR
7	Tablet compression machine	Cadmach Machinery, Ahmedabad
8	P^H meter	Elico LI 120
9	Dissolution test apparatus eight stage	LABINDIA, DS 8000
10	Monsanto Hardness tester	Campbell Electronics, model EIC-66, India
11	Sonicator	Loba Life
12	Roche Friabilator	Campbell Electronics, Mumbai

The following methodology was employed for the investigation:

5.1. PRE-FORMULATION STUDIES:

Pre-formulation may be described as a stage of development during which the physicochemical and biopharmaceutical properties of a drug substance are characterized. It is an important part of the drug development process. The information relating to drug development acquired during this phase is used for making critical decisions in subsequent stages of development. A wide variety of information must be generated to develop formulations rationally. Characterization of the drug is a very important step at the pre-formulation phase of product development followed by studying the properties of the excipients and their compatibility.

Pre-formulation testing is the first step in the rational development of dosage forms. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients.

The objective of pre-formulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced.

The use of pre-formulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product and at the same time provides the basis for optimization of the drug product quality.

5.1.1. ORGANOLEPTIC EVALUATION:

Organoleptic characters like color, odor, and taste of drug were observed and recorded using descriptive terminology.

5.1.2. DEVELOPMENT OF ANALYTICAL METHOD:

A survey of literature reveals that few analytical methods such as HPLC, UV/VIS spectrophotometric methods were reported for the estimation of Baclofen in formulations.

A simple, economic, convenient, reproducible and precise UV spectrophotometric method was employed for the assay as well as for the in-vitro dissolution studies.

UV Spectroscopy:

Preparation of Stock solution:

50mg of the drug (BCF) was accurately weighed and transferred to the 50mL volumetric flask. It was dissolved in sufficient quantity of 0.1N HCl and volume was made upto the mark with 0.1N HCl to obtain a stock solution of 1000µg/mL.

Determination of UV Absorption Maxima (λ_{max}) of Baclofen in 0.1N HCl :

From the stock solution, 50µL was transferred to a 5mL volumetric flask and the volume was made upto the mark with 0.1N HCl. The resulting solution containing 10µg/mL BCF in 0.1N HCl was scanned from 200-400 nm in 0.1N HCl as a blank using double beam UV/VIS spectrophotometer. The wavelength maximum was found to be at 220 nm.

Construction of the calibration curve:

An accurately weighed quantity of BCF (50mg) was dissolved in 50mL of 0.1N HCl to generate a stock solution having concentration of 1000µg/mL. From the stock solution, appropriate aliquots (10,20,30,40,50µL) were transferred to different volumetric flasks of 5ml capacity and made upto the volume with 0.1N HCl to obtain solutions with concentrations 2,4,6,8,10µg/mL respectively. The absorbance of the solutions were measured at 220nm against blank (0.1N HCl) using UV-visible spectrophotometer. The procedure was performed in triplicate to validate the calibration curve.

The absorbance values relating to different concentrations of BCF are given in **Table 6.1**. The absorbance was plotted against concentration of BCF as shown in **Fig. 6.1**.

5.1.3. DETERMINATION OF SOLUBILITY:

The following procedure was employed to determine the solubility of BCF in 0.1N HCl.

Excess of BCF was added to 5mL of 0.1N HCl in a 25mL stoppered conical flask and the mixture was shaken for 24 hours at room temperature (28±1^{o}C) on rotary shaker. After 24 hours of shaking 1mL aliquots were withdrawn at different time intervals and filtered immediately using a 0.45µ nylon disc filter. The filtered samples were diluted suitably and assayed for BCF by measuring the absorbance at 220nm. Shaking was continued until three consecutive estimations were same. The results are given in **Table 6.2.**

5.1.4. DRUG–EXCIPIENT COMPATIBILITY STUDY:

In the preparation of the tablets, drug and other excipients may interact as they are in contact with each other, which could lead to the instability of dosage form. Pre-formulation studies regarding the drug-excipient interaction are therefore very crucial in selecting appropriate excipients. FT-IR spectroscopy was employed to ascertain the compatibility between the drug and the selected excipents. The drug alone and physical mixtures of drug with excipients (1:1 ratio) were scanned separately in the range of 4000-500 cm^{-1} using KBr disc method.

Procedure*:* 1-2mg of the sample to be examined was triturated with 300-400 mg specified quantity of finely powered and dried potassium bromide. These quantities are usually sufficient to give a disc of 10-15mm diameter and pellet of suitable intensity by a hydraulic press. The Infrared spectrum was recorded by using FT-IR spectrophotometer and observed for characteristic peaks of the drug.

5.1.5. DETERMINATION OF MICROMERITIC PROPERTIES OF THE POWDER BLENDS:

The following tests were performed in-order to determine the flow properties of the powder blends.

Bulk Density[49] :

Bulk density is of great importance when one considers the size of a high-dose drug product or homogeneity of a low-dose formulation. The homogeneity of a low-dose formulation in which there are large differences in drug and excipient could lead to segregation.

Apparent Bulk density (g/mL) was determined by pouring (pre-sieved 18-mesh) gently 10g of the sample through a glass funnel into a 50mL graduated cylinder. Then after pouring the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as mL. The volume measure was called as the bulk volume and the bulk density was calculated by following formula.

Bulk density = Weight of powder / Bulk volume

Tapped Density [49] :

Tapped density (g/mL) was determined by pouring gently 10g of sample through a glass funnel into a 50mL graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained (100 taps).Volume occupied by the sample after tapping was recorded as the tapped volume (mL) and tapped density was calculated from the formula.

Tapped density = Weight of powder / Tapped volume

Carr's Compressibility Index(%) [49]:

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density.

High density powders tend to possess free flowing properties. A useful empirical guide is given by the Carr's index or compressibility index calculated from bulk density and tapped density.

Compressibility index = $1 - 100$

Where,

V = volume of powder blend before tapping

V_0 = volume of powder blend after 100 tappings

Hausner's ratio[49]:

Hausner's ratio provides an indication of the degree of densification which could result from vibration of the feed hopper. A lower value indicates better flow and vice versa.

Hausner's ratio = Tapped density /Bulk density

Angle of repose [49]:

The frictional force in a loose powder can be measured by the angle of repose. Angle of repose (θ) is the maximum angle between the surface of a pile of powder and horizontal

plane. It is usually determined by Fixed funnel method and is the measure of the flowability of powder/granules.

A funnel with 10mm inner diameter of stem was fixed at a height of 2cm over the platform. The sample was slowly passed along the wall of funnel, till the cone of the powder formed. Angle of repose was determined by measuring the height of the cone of powder and radius of the heap of the powder. Angle of repose was calculated using the following formula

$$\theta = \tan^{-1} (h/r)$$

where,

θ = Angle of repose

h = Height of the powder cone

r = Radius of the powder cone

The specifications for flow characteristics of powders are given in **Table 5.3.**

Table 5.3: Specifications for flow characteristics of powders

S.NO	TYPE OF FLOW	ANGLE OF REPOSE(°)	COMPRESSIBILITY INDEX (%)	HAUSNER'S RATIO
1.	Excellent	25-30	<10	1.00-1.11
2.	Good	31-35	11-15	1.12-1.18
3.	Fair (aid not needed)	36-40	16-20	1.19-1.25
4.	Passable (may hang up)	41-45	21-25	1.26-1.34
5.	Poor (must agitate, vibrate)	46-55	26-31	1.35-1.45
6.	Very poor	56-65	32-37	1.46-1.59
7.	Very very poor	>66	>38	>1.6

5.2. FORMULATION OF BACLOFEN SR FLOATING MATRIX TABLETS:

FORMULATION PLANNING:

Dose calculations involved in sustained drug delivery:

The amount of drug required in a sustained release dosage form, to provide a sustained drug level in the body is determined by the pharmacokinetics of the drug, the desired therapeutic level of the drug and the intended duration of action.

Pharmacokinetic parameters of Baclofen:

Elimination half life ($t_{1/2}$) = 4 hrs

Time to reach peak plasma concentration (tp) = 3 hrs

Calculations involved in the preparation of BCF sustained release floating tablets:

Conventional dose of Baclofen was found to be 5mg. This was considered as Initial dose (D_I).

Calculation of elimination rate constant:

Elimination rate constant (Kel) =$0.693/t_{1/2}$

=0.693/4

= 0.173/ hr

Calculation of zero order release rate constant:

Desired release rate from maintenance dose (k_0) = D_I x Kel

= 5 x 0.173

= 0.866 mg/hr

Calculation of maintenance dose:

Maintenance dose (D_M) = D_I x Kel x T [T= Time over which sustained dose is released]

= 5 x 0.173 x 24

= 20.79 mg

Calculation involved in correcting the initial dose:

Corrected D_I = D_I – [tp x D_I x Kel]

= 5-[3 x 5 x 0.173]

=2.40 mg

Calculation of total dose:

Total dose = D_M + corrected D_I

=20.79 +2.40

=23.19 mg

From the above calculations total dose for the sustained release of Baclofen for 24 hrs is 23.19 mg. The total dose was rounded to 23 mg for the convenience.

Tablets containing 23 mg of BCF were prepared with a total tablet weight of 200 mg. Considering the Pre-formulation studies carried out, direct compression technique has been employed to produce cost effective sustained release floating matrix tablets by effervescent approach.

Selection of polymers:

Hydrophilic swellable matrix polymers were selected as they were reported to have positive effect on floating behavior. Polymers are selected according to their drug retarding ability inorder to sustain the drug release for 24 hours. HPMC K4M, HPMC K15M, HPMC K100M, PEO WSR-301, PEO WSR-303 (Synthetic polymers) and xanthan gum, guar gum (natural polymers) were selected for the present investigation.

Selection of Effervescent agent:

Sodium bicarbonate (25-50%) is used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. When the tablet or granules come in contact with gastric acid (0.1N HCl), a chemical reaction occurs, CO_2 is evolved which gets entrapped in the swellable hydrophilic polymer matrix, which is responsible for the buoyancy of the formulation. Hence, sodium bicarbonate was selected as the effervescent agent in the formulation.

Selection of diluents:

Since Direct compression technique was employed, the choice of directly compressible diluents was important. Microcrystalline cellulose was selected as the filler or diluent owing to its multiple functionality as binder, disintegrant, compressibility and flowability. Microcrystalline cellulose also acts as wicking agent, that promotes the influx of water into the system and thereby improves the floating lag time of the FDDS. Moreover, it was proved[50] that microcrystalline cellulose is capable of swelling in contact with aqueous

fluids as simulated gastric fluid leading to an increase in the water uptake capacity, porosity of the matrix and consequently would enhance floating abilities. Of the various grades available, Avicel PH-102 was selected as it had been already reported to provide lower crushing strengths.

Selection of other ingredients:

To further improve the flow property of the blend, talc and magnesium stearate were used as lubricant and glidant respectively.

Formulae of floating matrix tablets of BCF are given in **Tables 5.4** and **5.5.**

Table 5.4: Formulae of floating matrix tablets of BCF:

Ingredients (%w/w of 200 mg tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
BCF	11.5	11.5	11.5	11.5	11.5	11.5	11.5	11.5	11.5
HPMC K100M	30	40	20	25	30	40	40	—	—
HPMC K15M	—	—	—	—	—	—	—	40	—
HPMC K4M	—	—	—	—	—	—	—	—	40
Sodium bicarbonate	25	25	10	10	10	10	12.5	12.5	12.5
Avicel PH -102	31.5	21.5	56.5	51.5	46.5	36.5	34	34	34
Talc	1	1	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1	1
Total	100	100	100	100	100	100	100	100	100

Table5.5: Formulae of floating matrix tablets of BCF:

Ingredients (%w/w of 200 mg tablet)	F10	F11	F12	F13	F14
BCF	11.5	11.5	11.5	11.5	11.5
Guar gum	40	—	—	—	—
Xanthan gum	—	40	—	—	—
PEO WSR-301	—	—	40	—	—
PEO-301+HPMC K100M(4:1)	—	—	—	40	—
PEO WSR-303	—	—	—	—	40
Sodium bicarbonate	12.5	12.5	12.5	12.5	12.5
Avicel PH-102	34	34	34	34	34
Talc	1	1	1	1	1
Magnesium stearate	1	1	1	1	1
Total	100	100	100	100	100

Procedure for the preparation of tablets:

BCF and all other ingredients were individually passed through sieve no≠60. Accurately weighed quantities of drug, polymer, sodium bicarbonate, MCC were transferred to a polythene bag and mixed homogenously for 15 minutes. The powder mix was then lubricated with talc and magnesium stearate. The powder blend was compressed into tablets on a single punch tablet machine using 8 mm flat round punches.

5.3. EVALUATION OF FLOATING TABLETS:

All the prepared tablets were evaluated for the following parameters:

5.3.1. Post-compression parameters:

Hardness[51]:

The hardness of the tablets was measured with a Monsanto hardness tester. The results reported were mean and standard deviation of 3 tablets for each formulation and expressed in kg/cm^2. Oral compressed tablets normally have a hardness of 4-9 kg/cm^2.

Friability (%F) [51]:

20 tablets from each batch were selected randomly and weighed. These pre-weighed tablets were subjected to friability testing using Roche friabilator for 100 revolutions. The tablets were subjected to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the %friability

%F = 1 – (Final weight / Initial weight) 100

A maximum weight loss of not more than 1% of the tablet weight during the friability test is generally considered acceptable.

Weight variation[51]:

20 tablets were randomly selected from each batch, weighed individually. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test if the weights of not more than 2 of tablets differ by more than the percentage listed in **Table 5.6** and no tablets differ in weight by more than double that percentage.

Table 5.6: Weight variation allowed for uncoated tablets

Average weight of tablet (mg)	Percentage difference allowed
≤ 130	10
130-324	7.5
>324	5

Drug content uniformity[51]:

Five tablets were weighed individually, then placed in a mortar and powdered with a pestle. Accurately weighed powder sample (200mg) equivalent to 23mg of BCF was transferred to a 100mL volumetric flask, and made upto volume 0.1N HCl. The contents of the volumetric flask were sonicated for 15 minutes inorder to extract the drug into 0.1N HCl. The solution was then filtered, suitably diluted with 0.1N HCl and the absorbance was measured at 220nm.The estimations were carried out in triplicate and the results are given in **Table 6.4.**

5.3.2. In-vitro buoyancy study [43]:

The study involves the determination of the floating lag time and total floating time. Floating lag time is the time required for the tablet to emerge onto the surface of the dissolution medium from the bottom of the dissolution vessel. The duration of floating (total floating time) is the time the dosage form constantly floats on the surface of the dissolution medium (excluding floating lag time).

Procedure: 3 tablets from each batch were transferred to USP XXI type- II dissolution apparatus containing 900 mL of 0.1N HCl. The study was performed at the paddle rotational speed of 50 rpm and temperature of 37±0.5°C.The floating lag time and the total floating time were recorded by visual observation using a stop watch. The results are given in **Table 6.5.**

5.3.3. In-vitro drug release study [43]:

The tablet samples were subjected to in-vitro dissolution study using USP XXI type II (Paddle method) Dissolution rate test apparatus at a temperature of 37±0.5°C and 50 rpm speed. 900 mL of 0.1N HCl (pH-1.2) was used as the dissolution medium. Aliquot equal to 5mL was withdrawn at specific time intervals for 24 hours. The dissolution media

volume was complimented with fresh and equal volume of blank media (0.1N HCl). The aliquots were filtered and assayed for BCF by measuring the absorbance at 220 nm against blank (0.1N HCl). The dissolution experiments were carried out in triplicate. The results are given in **Tables 6.6-6.20.**

Table 5.7: Dissolution parameters

Apparatus used	USP XXI tablet dissolution test apparatus-II
Dissolution medium	0.1N HCl (pH- 1.2)
Dissolution medium volume	900 mL
Temperature	37±0.5ºC
Paddle speed	50 rpm
Sample volume withdrawn	5 mL
Sampling intervals (hrs)	0.5,1,2,3,4,6,8,10,12,16,24 .
Absorbance measured at	220 nm

5.4. MATHEMATICAL MODEL FITTING OF OBTAINED DRUG RELEASE DATA:

The rate and mechanism of release of BCF from the prepared tablets were analysed by fitting the dissolution data into

Zero order kinetics

First order kinetics

Higuchi model

Korsmeyer –Peppas model

5.4.1 Zero order kinetics[52]:

This equation describes the systems where the release rate is independent of the concentration of the dissolving species. The equation describing the kinetics is given below

$$Q_t = Q_o + K_o t$$

Where

Q_t = amount of drug dissolved in time t

Q_o = initial amount of drug in the solution

K_o = zero order release constant

For zero order release kinetics, the graph was plotted between cumulative percent of drug released versus time.

Dosage forms following this profile, release same amount of drug per unit time, and it is the ideal method of release for a sustained release product.

5.4.2. First order kinetics[53]:

Gibaldi and Feldman first proposed the application of this model to drug dissolution studies in 1967. The First order equation describes the release from systems where the release rate is dependent upon the concentration of the dissolving species. The equation is given below:

Where, Co is the initial concentration of the drug, K is the first order rate constant, and t is the time. The data obtained are plotted as log cumulative % of drug remaining Vs time which would yield a straight line with a slope of –K/2.303.

For first order release kinetics, the graph was plotted between log cumulative percent of drug remaining versus time.

5.4.3. Higuchi model[54]:

Higuchi first proposed this model to describe dissolution of drug in suspension from ointment bases, but is widely applicable to other types of dosage forms. The equation is given below:

Where Q is the amount of drug released at time t per unit area A, C is the initial drug concentration, Cs is the drug solubility in the matrix media and D is the diffusivity of the drug molecules in the matrix substance.

Simplified Higuchi model

$$F_t = K_H \times t^{1/2}$$

Where K_H is the Higuchi dissolution constant. For Higuchi model, the graph was plotted between cumulative percent of drug released versus square root of time. The linearity of the graph indicates the diffusion controlled release.

5.4.4. Korsmeyer –Peppas model[55]:

Korsmeyer and Peppas, in 1983 derived a mathematical equation which described the mechanism of drug release from a polymeric system. It is also known as Power law which is more comprehensive in describing the drug release mechanism as compared to Higuchi model. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer –Peppas model

$$M_t/M_\infty = K\, t^n$$

Where M_t/M_∞ is a fraction of drug released at time t, K is the release rate constant and 'n' is the release exponent. For Korsmeyer-Peppas model, the graph was plotted between log cumulative percent of drug released versus log time. From the graph, the value of 'n' characterizes the release mechanism of drug as described in **Table.5.8**.

Table 5.8: Interpretation of drug release mechanism from drug release data (Peppas, 1983).

Exponent, 'n'			Drug release Mechanism
Thin film	Cylinder	Sphere	
0.5	0.45	0.43	Fickian Diffusion
0.5<n<1.0	0.45<n<0.85	0.43<n<0.85	Non – Fickian Diffusion/Anomalous Transport
1.0	0.89	0.85	Zero order/ Case II transport

When the exponent '*n*' takes a value of 1.0, the drug release rate is independent of time. This case corresponds to zero-order release kinetics (also termed as case II transport). Here the relaxation process of the macromolecules occurring upon water imbibitions into the system is the rate-controlling step. When n = 0.5, Fickian diffusion is the drug release mechanism. Thus, Equation has two distinct physical meanings in the two special cases of n=0.5 (indicating diffusion-controlled drug release) and n=1 (indicating swelling-controlled drug release). Values of *n* between 0.5 and 1.0 can be regarded as an indicator for the superposition of both phenomena (anomalous transport). It has to be kept in mind that the two extreme values for the exponent '*n*' 0.5 and 1.0 are only valid for slab geometry.

5.5. OPTIMIZATION OF TABLET FORMULATION:

Based upon the buoyancy characteristics and percent cumulative drug release, the optimised formulation was selected.

5.6. RELEASE PROFILE COMPARISON:

The release profile of the optimized formulation was compared with the release profile of the marketed formulation.

Determination of Similarity factor, f_2 value[56]:

This factor was introduced by Moore and Flanner and has been adopted by the centre for Drug Evaluation and Research (US FDA) and by Human Medicines Evaluation Unit of the European Agency for the Evaluation of Medicinal Products (EMEA) as a criterion for the assessment of the similarity between two dissolution profiles. It is included in various guidance documents. The similarity factor f_2 as defined by FDA and EMEA is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) differences of percent drug dissolved between the test and reference products:

/ ! · 100$

Where, n is the number of dissolution time points.

Rt and Tt are the reference and test dissolution values (mean of at least 12 dosage units) at time t.

FDA recognizes the release profiles to be similar when the f_2 value is between 50 and 100.

CHAPTER 7

RESULTS

AND

DISCUSSION

Spasticity, a condition in which certain muscles are continuously contracted, affects over 12 million worldwide. Generally, spasticity is associated with common neurological disorders like multiple sclerosis, stroke, cerebral palsy and spinal cord injury. Baclofen is the largest prescribed drug for this indication, world wide.

The half-life of the drug is ~2.5 to 4 hrs in plasma which requires frequent dosing (conventional tablets). The patient compliance can be improved and the side effects can be minimized with the once-daily formulation.

Baclofen is difficult to formulate into sustained release dosage forms because it has an absorption window in upper G.I. tract and on arrival to colon (or even before) its absorption is diminished or nonexistent resulting in low bioavailability. Hence, in the present investigation, efforts were made to increase the residence time of Baclofen at the absorption window by formulating sustained release gastro-retentive floating tablets inorder to improve the bioavailability considering the fact that Baclofen is stable under gastric condition.

The results of the investigation are summarized as follows:

6.1. PREFORMULATION STUDIES:

6.1.1. Organoleptic evaluation:

Baclofen is a white crystalline powder, virtually odorless, with slightly bitter taste.

6.1.2. Analytical method:

Determination of UV Absorption Maxima (λ_{max}) of Baclofen in 0.1N HCl :

A 10 µg/mL solution of Baclofen in 0.1N HCl was scanned from 200-400 nm using double beam UV/VIS Spectrophotometer. The wavelength maximum was found to be 220 nm as shown in **Fig.6**.

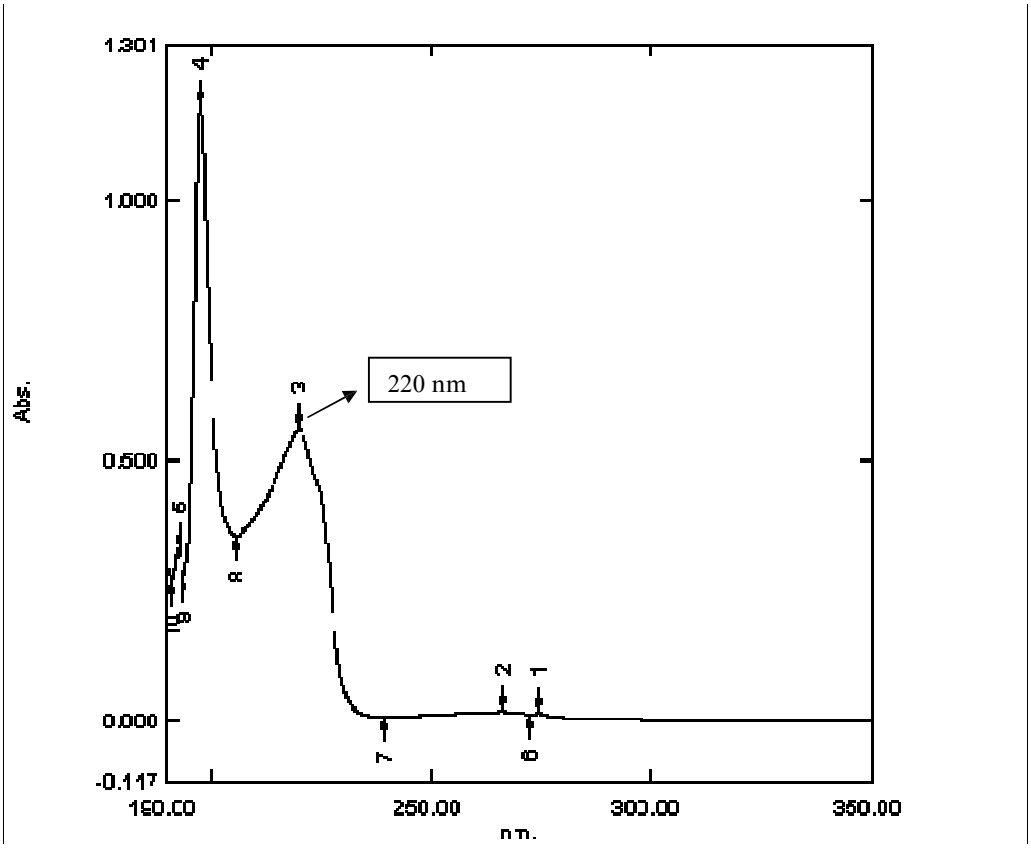


Fig 6: **Scanning graph of BCF in 0.1N HCl**

Standard calibration curve of Baclofen in 0.1N HCl (pH-1.2):

The dissolution medium employed for the gastro-retentive tablets is 0.1N HCl (pH-1.2) (Simulated gastric fluid). Hence, the calibration curve of BCF was constructed in 0.1N HCl.

2,4,6,8,10 µg/mL solutions of Baclofen in 0.1N HCl were prepared and the absorbance values relating to different concentrations of BCF were measured at 220nm against blank (0.1N HCl) using UV/VIS spectrophotometer. The absorbance values relating to different concentrations of BCF are given in **Table 6.1**. The absorbance was plotted against concentration of BCF as shown in **Fig. 6.1**.

Table 6.1: Calibration curve data for the estimation of BCF in 0.1N HCl

Concentration (µg/mL)	ABSORBANCE(nm)			
	Trial -I	Trial -II	Trial -III	Mean± S.D
2	0.061	0.063	0.05	0.058±0.007
4	0.098	0.106	0.098	0.101±0.005
6	0.155	0.167	0.154	0.159±0.007
8	0.203	0.228	0.195	0.209±0.017
10	0.261	0.279	0.253	0.264±0.013

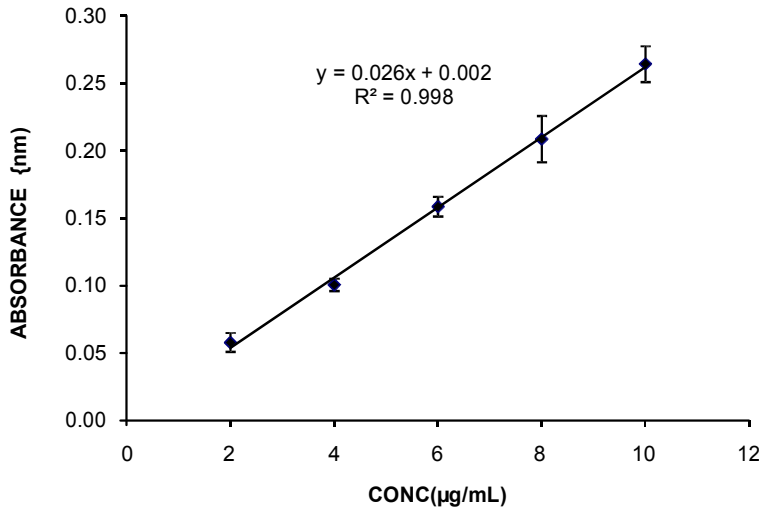


Fig 6.1: Standard calibration curve of BCF in 0.1N HCl

The present analytical method obeyed Beer-Lambert's law in the concentration range of 2-10 µg/mL. The R^2 (correlation coefficient) value for the linear regression equation was found to be 0.998. The linear regression equation was found to be

$$y=0.026x+0.002$$

The selected method was found to be sensitive, accurate, precise and reproducible and used for the estimation of Baclofen in the present investigation.

6.1.3. Solubility study:

The dissolution medium employed for the gastro-retentive tablets is 0.1N HCl (pH-1.2) (Simulated gastric fluid). Hence, the solubility of Baclofen in 0.1N HCl was determined inorder to verify whether sink condition can be maintained in the in-vitro dissolution process employing 0.1N HCl as the dissolution medium. The results of the solubility study are reported in **Table 6.2**.

Table 6.2: Solubility determination of BCF in 0.1N HCl

MEDIUM	ABSORBANCE (nm)	DILUTION FACTOR	SOLUBILITY (mg/mL)
0.1N HCl	0.657	1000	25.2

Practically, the solubility of Baclofen in 0.1 N HCl (Simulated gastric fluid) was found to be 25.2 mg/mL.

From the solubility study, it was evident that the sink condition can be maintained in the in-vitro dissolution process employing 0.1N HCl as the dissolution medium.

6.1.4. Drug- excipient compatibility study:

FT-IR interpretation[40]:

FT-Infrared spectroscopy was employed to find out the compatibility of drug with the excipients. This study was carried out to find out the possible interaction between the selected drug BCF and the excipients. FT-IR spectrum of Baclofen showed the following characteristic peaks at 1093cm^{-1} (due to –C-Cl), 1526 cm^{-1} (due to -COOH), and 1626 cm^{-1} (due to $–NH_2$). These prominent peaks of drug were also present in the IR spectra of physical mixtures of drug with various excipients, thus revealing compatibility of the selected drug with the excipients. The FT-IR spectra are shown in **Figs. 6.2-6.13**.

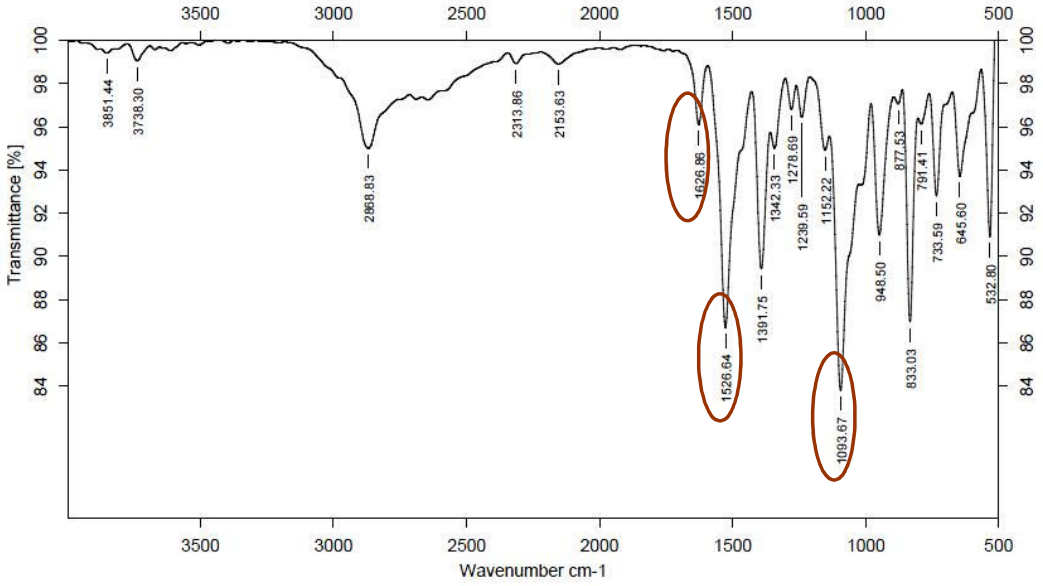


Fig 6.2: FT-IR spectrum of BCF

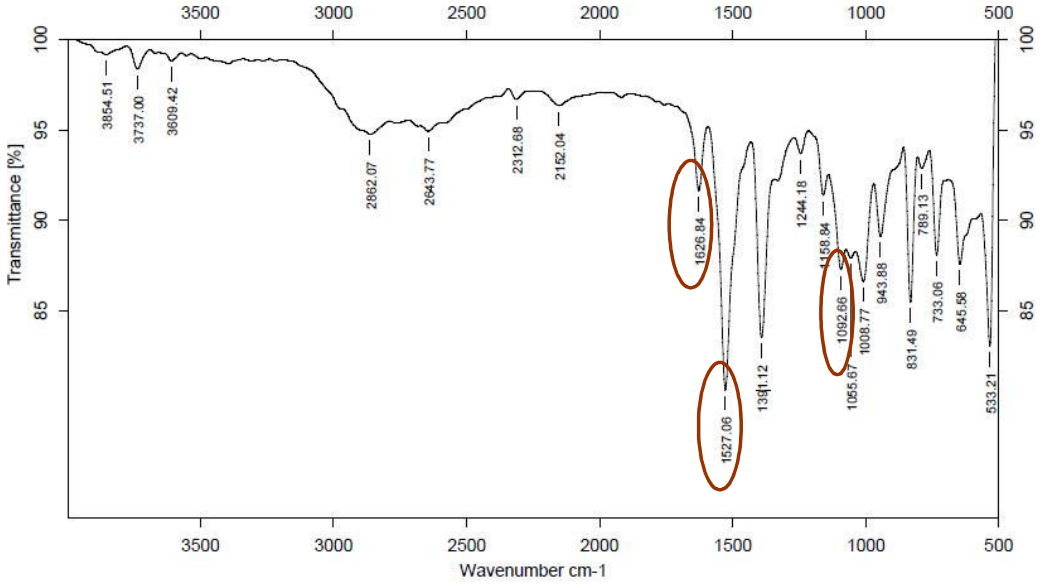


Fig 6.3: FT-IR spectrum of BCF-HPMC K100M

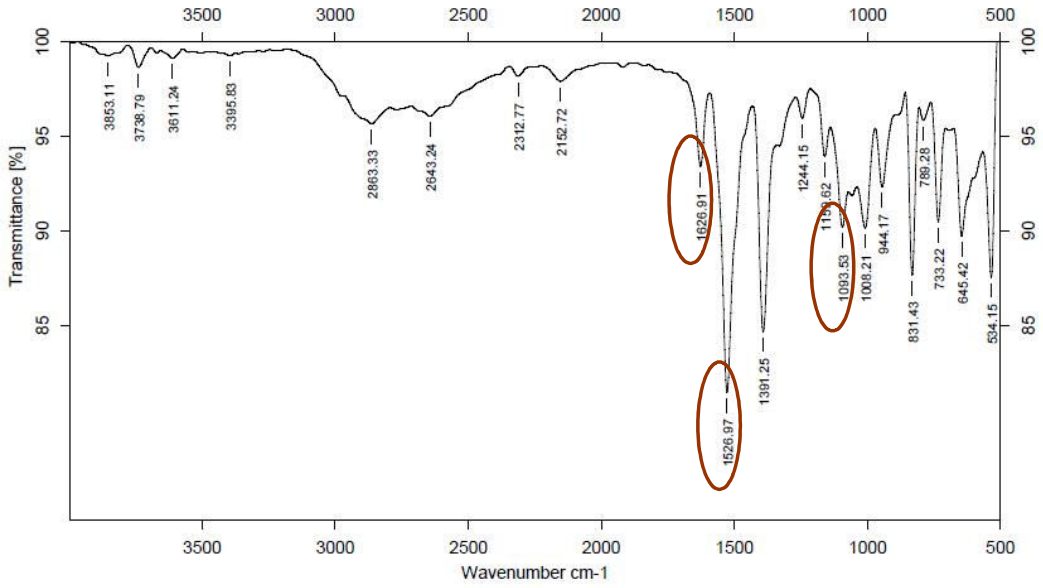


Fig 6.4: FT-IR spectrum of BCF-HPMC K4M

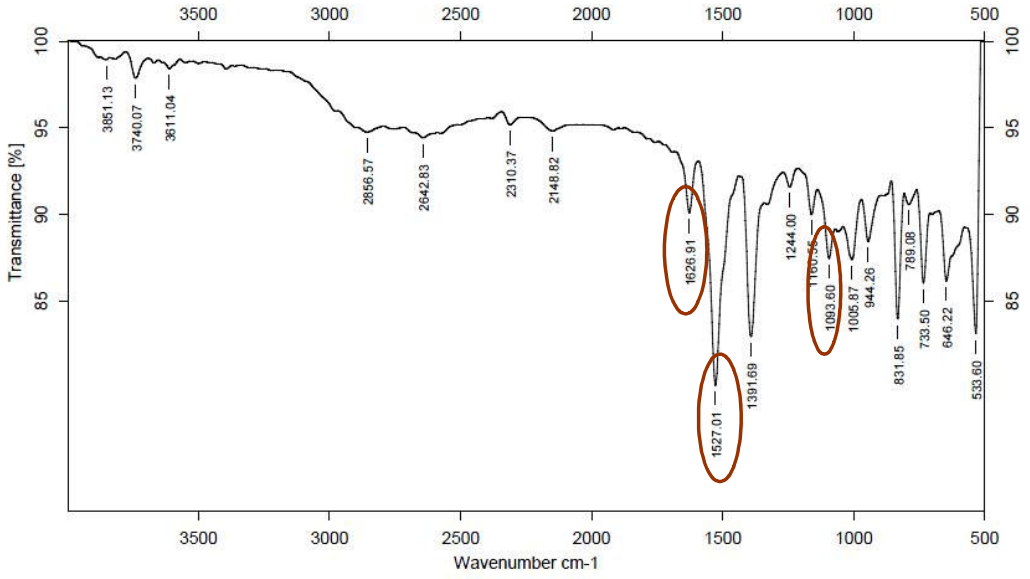


Fig 6.5: FT-IR spectrum of BCF-HPMC K15M

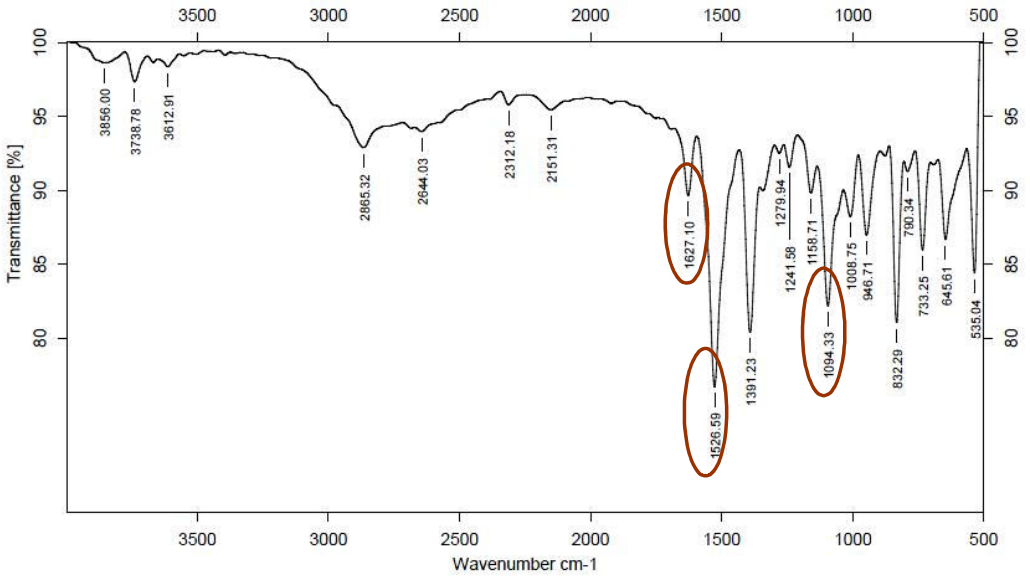


Fig 6.6: FT-IR spectrum of BCF-PEO WSR-301

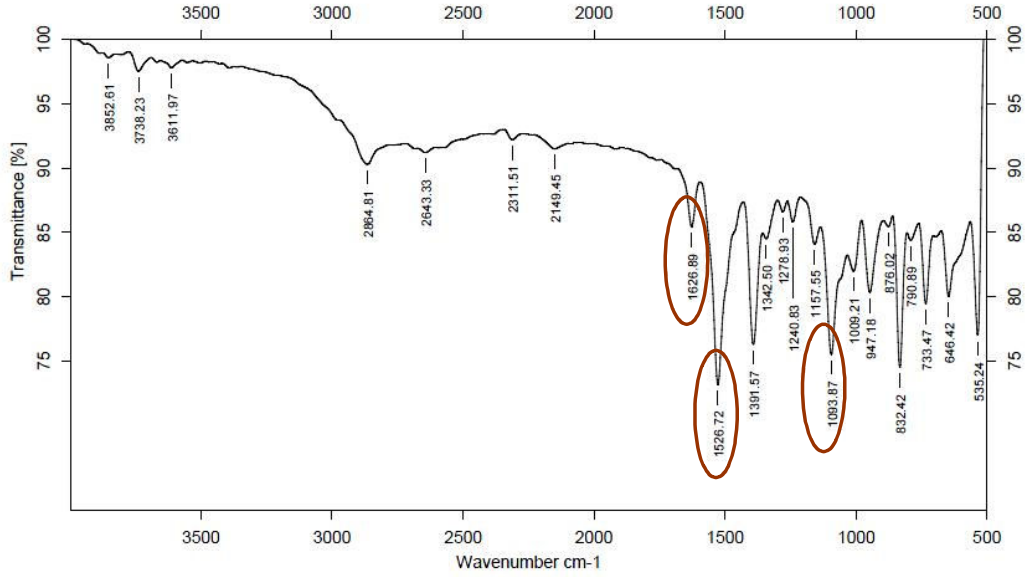


Fig 6.7: FT-IR spectrum of BCF-PEO WSR-303

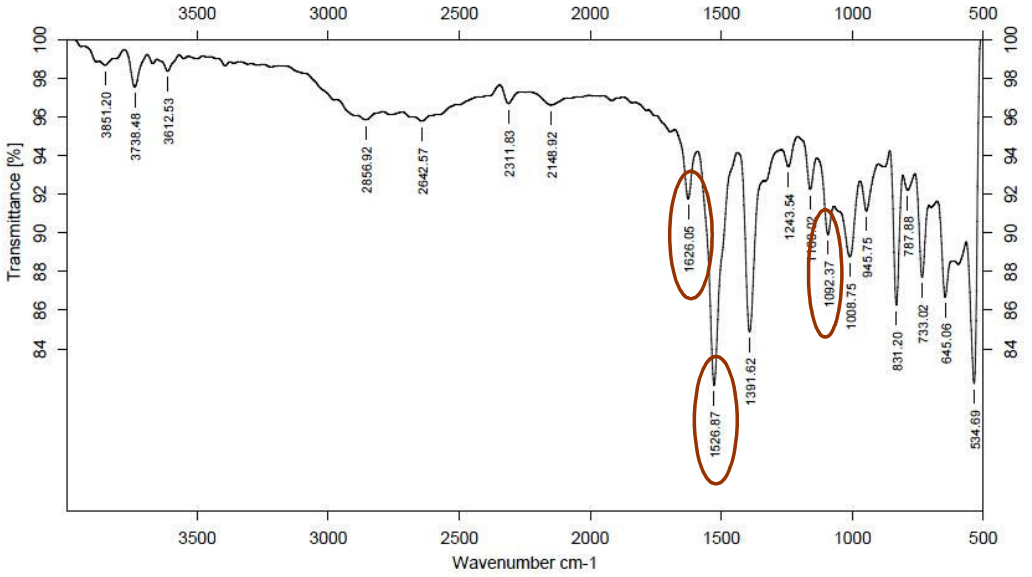


Fig 6.8: FT-IR spectrum of BCF- Xanthan gum

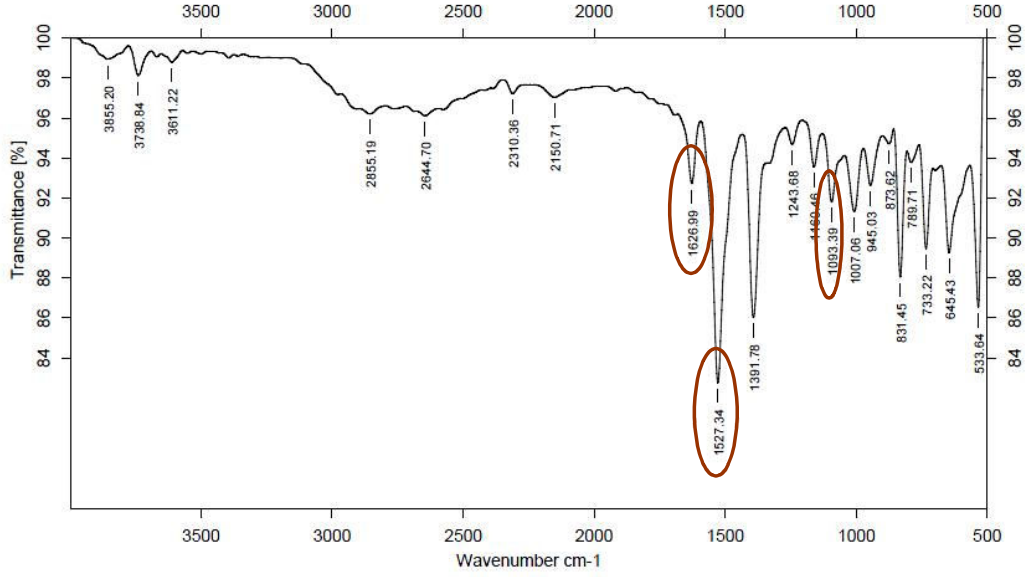


Fig 6.9: FT-IR spectrum of BCF- Guar gum

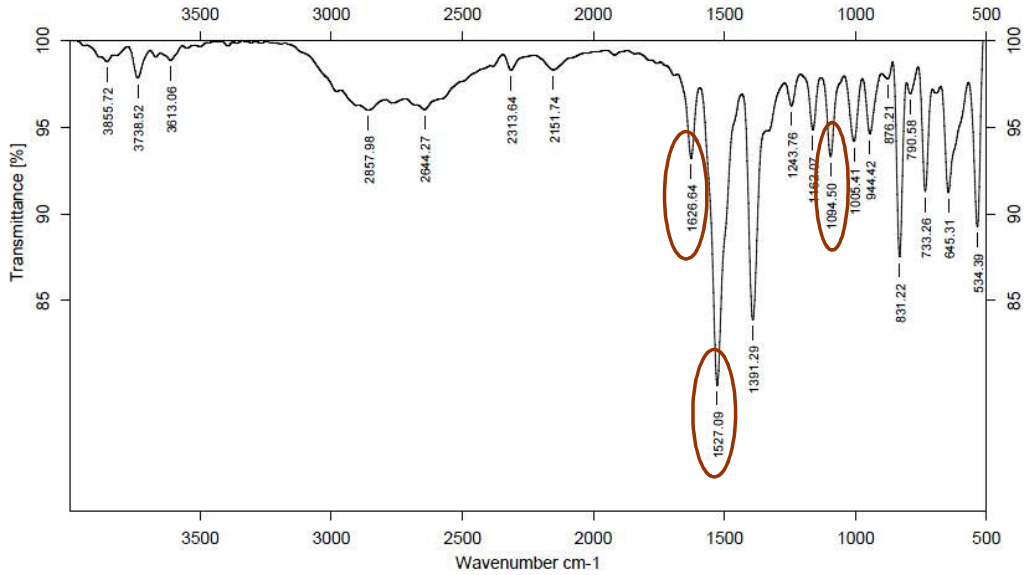


Fig 6.10: FT-IR spectrum of BCF-Sodium bicarbonate

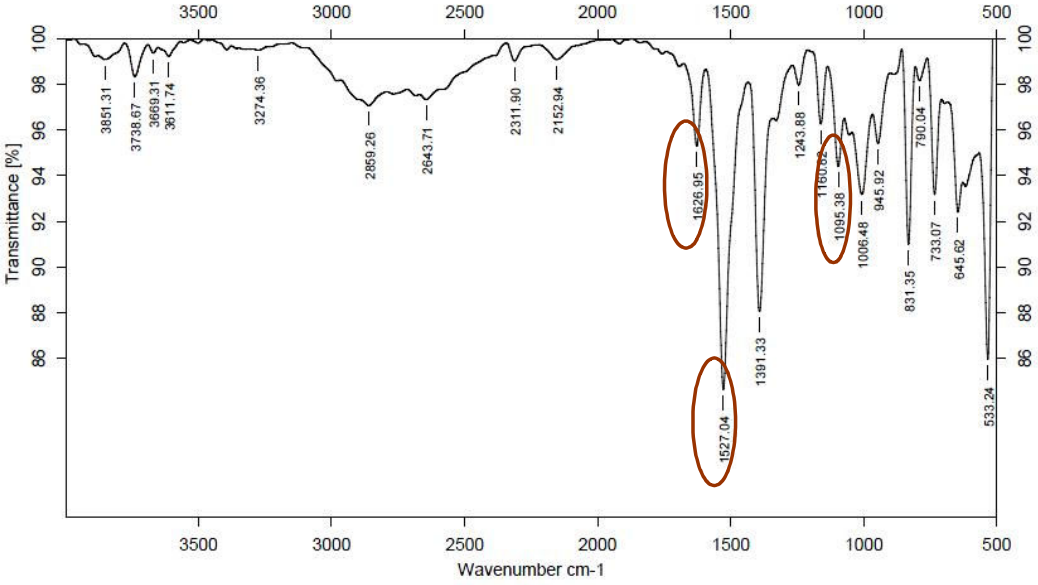


Fig 6.11: FT-IR spectrum of BCF-MCC

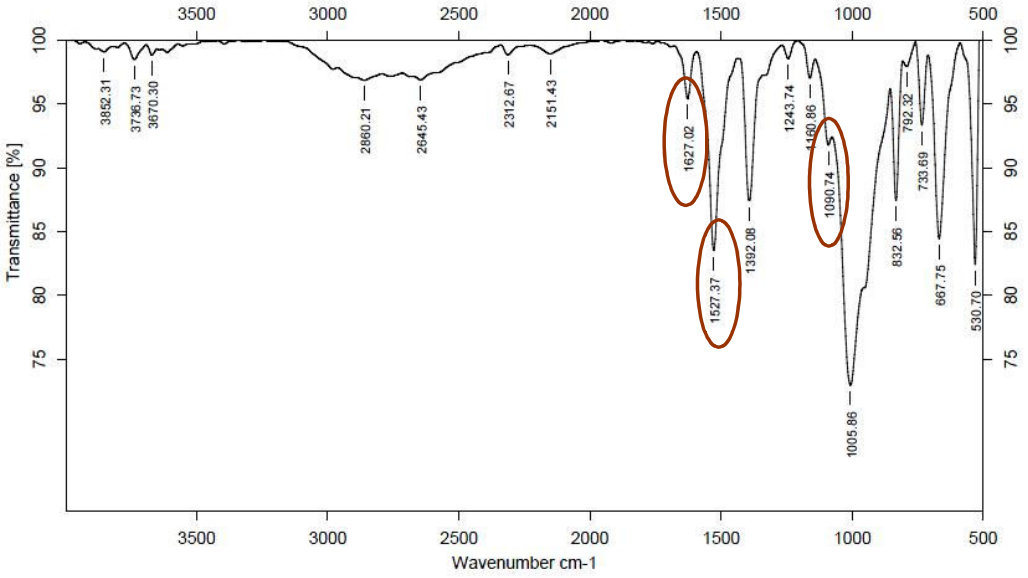


Fig 6.12: FT-IR spectrum of BCF-Talc

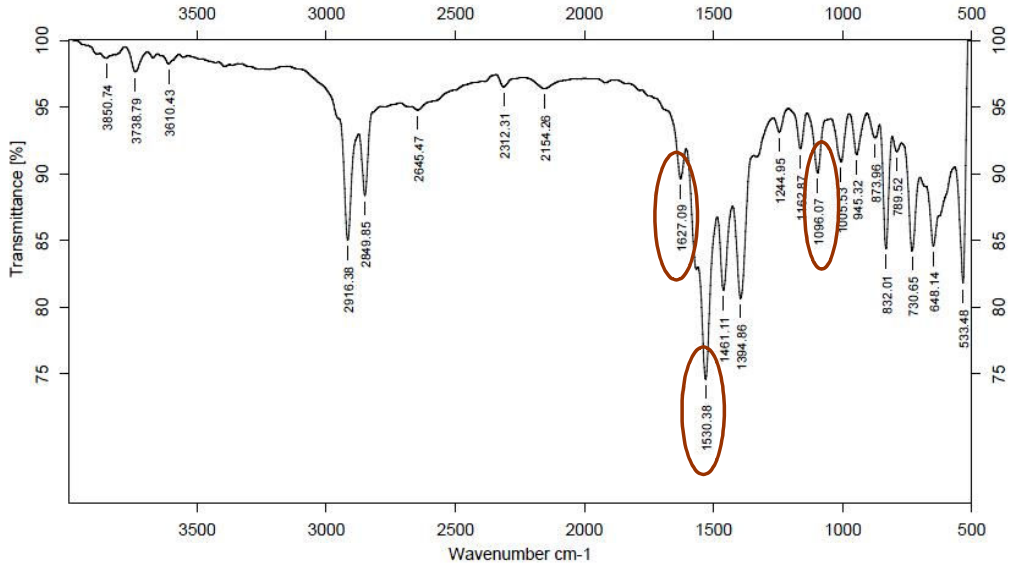


Fig 6.13: **FT-IR spectrum of BCF-Magnesium stearate**

6.1.5. Determination of micromeritic properties of powder blends:

The powder blends of the formulations were evaluated for micromeritic properties like bulk density, tapped density, Carr's compressibility index and Hausner's ratio. The results are reported in **Table 6.3.**

Table 6.3: Micromeritic properties of powder blends of various formulations

Batch code	Angle of repose(θ)	Bulk Density(g/mL)	Tapped density(g/mL)	Carr's index(%)	Hausner's ratio
F1	34.90°	0.222	0.256	13.28	1.15
F2	32.34°	0.266	0.310	14.19	1.17
F3	34.54°	0.258	0.291	11.30	1.13
F4	33.18°	0.281	0.321	12.46	1.14
F5	32.77°	0.242	0.279	13.26	1.15
F6	31.32°	0.240	0.280	14.28	1.17
F7	32.54°	0.250	0.290	13.79	1.16
F8	33.30°	0.298	0.345	13.62	1.15
F9	32.80°	0.266	0.309	13.91	1.16
F10	33.04°	0.311	0.355	12.39	1.14
F11	34.18°	0.240	0.270	11.11	1.13
F12	33.43°	0.296	0.342	13.45	1.16
F13	34.23°	0.311	0.356	12.64	1.14
F14	32.31°	0.250	0.287	12.89	1.15

Bulk density:

The bulk density of the powder blends ranged between 0.222-0.311 g/mL.

Tapped density:

The tapped density of the powder blends ranged between 0.256-0.356 g/mL.

Carr's compressibility index:

If the compressibility index of the powder blend ranged between 11-15 %, it indicates good flow property. All the blends were within the range (11.11-14.28%), indicating that the blends exhibit good flow property.

Hausner's ratio:

The Hausner's ratio of the powder blends ranged between 1.13-1.17. It indicates good flow property of the blends.

Angle of repose(θ) :

The angle of repose for all the powder blends ranged between 31.32°-34.90°, indicating good flow property of the blends.

From the results, the powder blends of all the formulations were found to possess good flow property. Hence, direct compression technique was employed for the preparation of BCF tablets.

6.2. EVALUATION OF BCF FLOATING TABLETS:

The floating tablets of BCF were prepared by direct compression technique using effervescent approach.

All the prepared tablets were evaluated for the following parameters:

6.2.1. Post-compression parameters:

The formulated tablets were evaluated for various physico-chemical parameters like hardness, weight variation, friability, drug content uniformity. The results are reported as mean ± S.D. The results are reported in **Table 6.4.**

Table 6.4: Post-compression parameters of BCF floating tablets

Formulations	Avg. wt(mg) Mean ± S.D	Hardness (kg/cm^2)	Friability (% wt. loss)	Drug Content (%)
F1	197±1.3	6.83±0.29	0.46	96.11±0.76
F2	197±1.8	7.0±0.5	0.29	95.89±0.42
F3	198±2.5	4.17±0.29	0.51	98.47±0.83
F4	199±1.2	4.33±0.29	0.21	97.0±0.34
F5	197±1.6	4.17±0.29	0.41	97.12±0.36
F6	196±1.4	4.17±0.29	0.57	101.4±0.52
F7	199±1.7	4.5±0.5	0.64	99.0±0.40
F8	197±2.2	4.0±0.00	0.57	98.39±0.66
F9	198±2.6	4.17±0.29	0.42	96.86±0.37
F10	201±1.9	4.33±0.29	0.36	98.64±0.21
F11	197±1.2	4.5±0.5	0.52	97.89±0.48
F12	197±2.9	4.33±0.29	0.45	96.5±2.22
F13	198±1.3	4.17±0.29	0.80	95.53±1.39
F14	199±0.7	4.5±0.00	0.43	97.09±1.59

Hardness:

Oral compressed tablets normally have a hardness of 4-9 kg/cm^2. The hardness of the formulations ranged between 4.0- 7.0 kg/cm^2. No significant difference in hardness values of all batches of tablets prepared was observed. So, all formulations pass the test.

Weight variation test:

Twenty tablets of each formulation were selected randomly and weighed individually using an electronic balance to check the weight variation as per USP. Not more than two tablets should cross the preferred deviation. The acceptable deviation is 7.5%. All the formulated tablets were within 7.5% deviation. So, all tablets pass the test.

Friability:

The test was performed to evaluate the ability of the tablets to withstand abrasion during packing, handling and transporting. A maximum weight loss of not more than 1% of the tablet weight during the friability test is generally considered acceptable. The weight loss of all the tablets was within the limit (0.21%-0.80%). The percentage loss in weight of the formulations was reported in **table.6.4**.

Drug content uniformity:

This test is highly essential for determining the actual amount of drug present in the tablets. For the drugs in tablet form, the official potency range that is permitted is not less than 95% and not more than 105% of the labeled amount. From the results, the percentage of BCF in all the formulations ranged from 95.53±1.39% – 101.4±0.52%. So, all the tablet formulations were found to possess the claimed amount of the drug.

6.2.2. In-vitro Buoyancy study:

The study was performed using USP XXI type-II (paddle) dissolution apparatus containing 900mL of 0.1N HCl as the dissolution medium. The study was performed at the paddle rotational speed of 50 rpm and a temperature of 37±0.5°C.The floating lag time and the total floating time were recorded by visual observation using a stop watch.
The results are reported in **Table 6.5** and represented as bar graphs (**Figs. 6.14-6.15**).

Table 6.5: Buoyancy determinations of BCF floating tablets

FORMULATIONS	PARAMETERS	
	FLT(SECONDS)	TFT(HOURS)
F1	73.33±15.28	24
F2	210.67±21.01	24
F3	14.67±1.16	24
F4	20±2	24
F5	51±13.12	24
F6	160±26	24
F7	25.67±3.77	24
F8	28.33±1.53	24
F9	584±14.42	24
F10	458±8.19	24
F11	20.33±6.03	24
F12	31.67±10.02	12
F13	41±3.61	12
F14	53.33±9.45	14
F.M	63.67±4.01	24

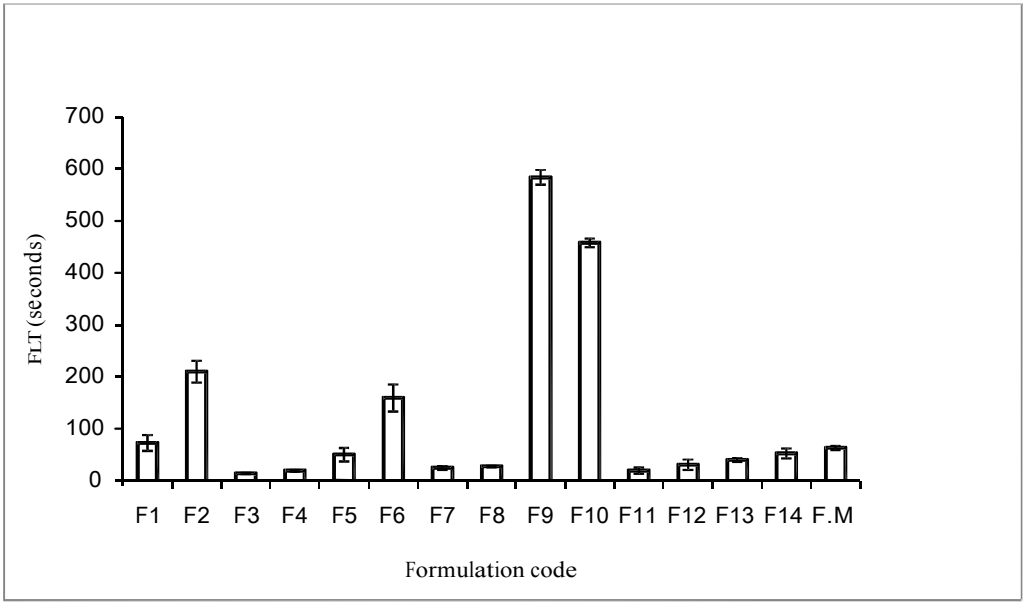


Fig 6.14: **Floating lag time of the Formulations**

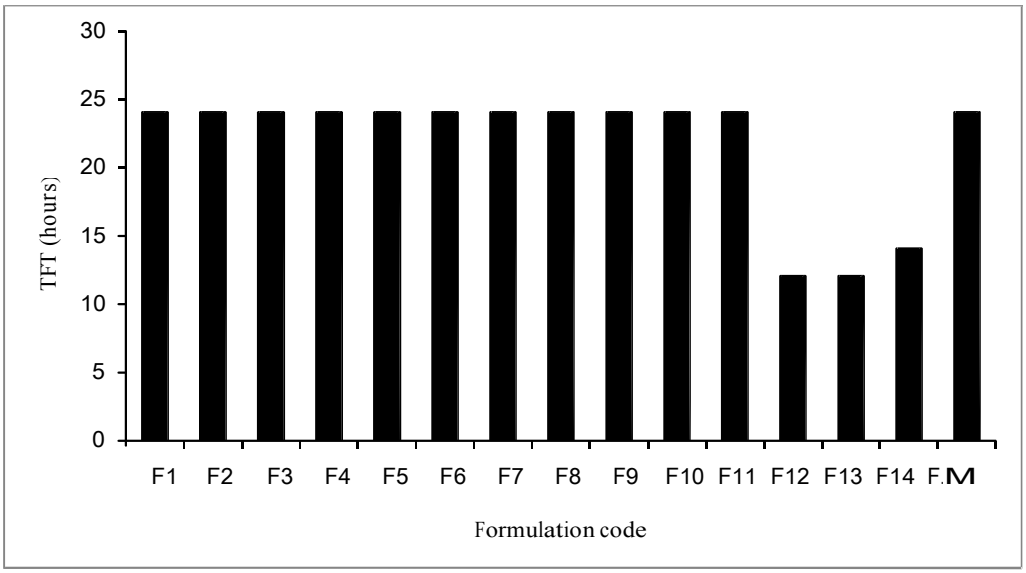


Fig 6.15: **Total floating time of the Formulations**

All the tablets were prepared by effervescent approach. Sodium bicarbonate was added as the gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in the presence of dissolution medium (0.1N Hydrochloric acid).

It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer thus decreasing the density of the tablet below 1 and tablet becomes buoyant.

The duration of buoyancy of all the formulations (including marketed product) was found to be 24h except for the formulations (F12,F13,F14) which were formulated using different grades of PEO. The reason for the less duration of buoyancy of these formulations may be due to the failure of the polymer in maintaining the matrix integrity throughout the dissolution process. Hence, these formulations were rejected.

The buoyancy lag time of all the formulations (including marketed product) ranged between 14.67±1.16 – 584±14.42 seconds. Formulation F3 prepared using HPMC K100M-20% and sodium bicarbonate-10% exhibited very less floating lag time (14.67±1.16 seconds) and formulation F9 prepared using HPMC K4M-40% and sodium bicarbonate 12.5%, exhibited very high floating lag time (584±14.42seconds).

Formulations F1-F7 were prepared using polymer HPMC K100M.The initial formulations F1 and F2 were formulated using sodium bicarbonate-25% with a hardness

of 7 kg/cm^2. The formulations exhibited higher lag times of 73.33±15.28 seconds and 210.67±21.01 seconds respectively. This may be due to the greater hardness of the tablets, which prevents the quick entry of the dissolution medium into the matrix which is responsible for the acid-base reaction and thereby buoyancy.

Hence, the further formulations were formulated with a hardness of 4 kg/cm^2. Formulations F3-F6 were formulated using sodium bicarbonate-10% and different concentrations of the polymer (HPMC K100M). It was observed that, with the increase in the polymer concentration, the floating lag time increased gradually. The increase in polymer concentration would possibly prevent the entry of media into the tablet matrix and prolong the floating lag time. The influence of polymer concentration on the floating lag time was clearly evident from the **Fig. 6.16.**

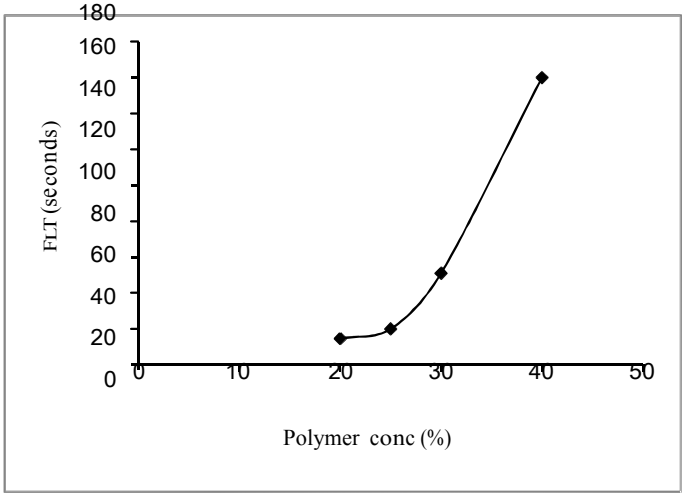


Fig 6.16: Effect of polymer concentration on the Floating lag time

The floating lag time of formulation F6 was found to be 160±26 seconds. Hence, in order to further decrease the floating lag time, for formulation F7 the amount of sodium bicarbonate was increased to 12.5%.

Formulation F7 exhibited optimum floating lag time of 25.67±3.77 seconds. Hence, the optimum amount of sodium bicarbonate was fixed to be 12.5%, which was used in rest of the formulations (F8-F14).

With formulations containing the same amount of polymer of the same grade (F6,F7), floating lag time decreased with increase in concentration of sodium bicarbonate. This

finding also supported by study of ***Baumgartner et al***.[57] who reported that incorporation of sodium bicarbonate in the matrix system helps to improve floating properties by reacting with gastric fluid when dosage form comes in contact with media.

With formulations containing the same amount of polymer of the same grade (F2,F6), floating lag time decreased with decrease in the hardness of the tablets. Formulation F2 with sodium bicarbonate-25% (hardness-7 kg/cm^2) exhibited higher lag time than the formulation F6 with sodium bicarbonate-10% (hardness-4 kg/cm^2).Even though more amount of sodium bicarbonate was used in formulation F2, the FLT was high. From the finding, it can be concluded that hardness of the tablet is crucial for achieving optimal buoyancy lag time.

Formulations F9 and F10 containing HPMC K4M and Guar gum respectively exhibited very high lag times. The reason may be due to the inadequate gel strength of the HPMC K4M (escape of the CO_2 gas at the initial stage from the weak gel layer) and F10 with guar gum exhibited high lag time due to the erosion of the matrix at the initial stage of dissolution(there is no quick formation of gel layer for the entrapment CO_2 gas).

Formulation F11 prepared using xanthan gum-40% and sodium bicarbonate-12.5% exhibited floating lag time of 20.33±6.03 seconds and total floating time of 24 hours. The marketed formulation (F.M) exhibited floating lag time of 63.67±4.01 seconds and total floating time of 24 hours.

From the Buoyancy study, it can be concluded that optimum amount of sodium bicarbonate and polymer with sufficient gel strength are essential to achieve optimum in-vitro buoyancy.

6.2.3. In-vitro drug release study:

All the formulations (F1-F14) and the marketed formulation were subjected to in-vitro dissolution testing.

In-vitro dissolution study was carried out for all the batches of matrix tablets using USP XXI type-II (paddle type) dissolution apparatus at temperature 37 $\pm$ 0.5°C and 50 rpm speed. 900 mL of 0.1N HCl was used as the dissolution medium. The drug release data is given in **Tables 6.6-6.20** and the dissolution profiles of the formulations are shown in **Figs. 6.17-6.31.**

Table 6.6: Mean ± S.D percent of BCF released from BCF floating tablets (F1)

Time(hrs)	% BCF released			Mean± SD
	1	2	3	
0	0	0	0	0
0.5	24.09	24.68	23.65	24.14±0.52
1	29.29	30.18	28.70	29.39±0.74
2	37.57	38.75	37.13	37.82±0.84
3	44.08	45.41	43.19	44.23±1.12
4	52.22	52.81	51.92	52.32±0.45
6	59.91	60.95	59.47	60.11±0.76
8	69.82	70.26	68.19	69.43±1.09
10	74.71	75.89	76.04	75.55±0.73
12	83.28	84.17	82.99	83.48±0.62
16	93.93	94.97	95.41	94.77±0.76
24	---	---	---	---

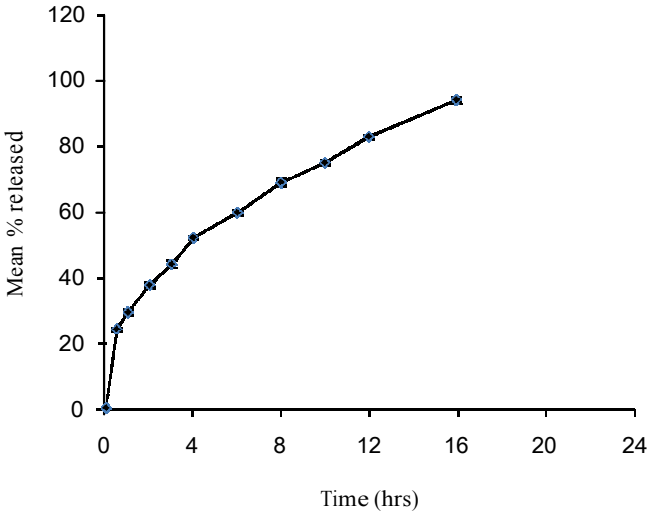


Fig 6.17: *In-vitro* dissolution profile of BCF from F1

Table 6.7: Mean ± S.D percent of BCF released from BCF floating tablets (F2)

Time(hrs)	% BCF released			Mean± SD
	1	2	3	
0	0	0	0	0
0.5	18.18	17.44	18.47	18.03±0.53
1	26.77	25.73	27.36	26.62±0.82
2	34.61	33.87	35.20	34.56±0.67
3	43.63	43.04	41.86	42.85±0.90
4	49.26	48.37	50.29	49.31±0.96
6	57.54	56.65	57.99	57.39±0.68
8	61.10	61.98	60.95	61.34±0.56
10	69.08	68.34	69.67	69.03±0.67
12	74.12	74.26	74.71	74.36±0.31
16	83.14	83.58	84.47	83.73±0.68
24	96.45	95.41	96.01	95.96±0.52

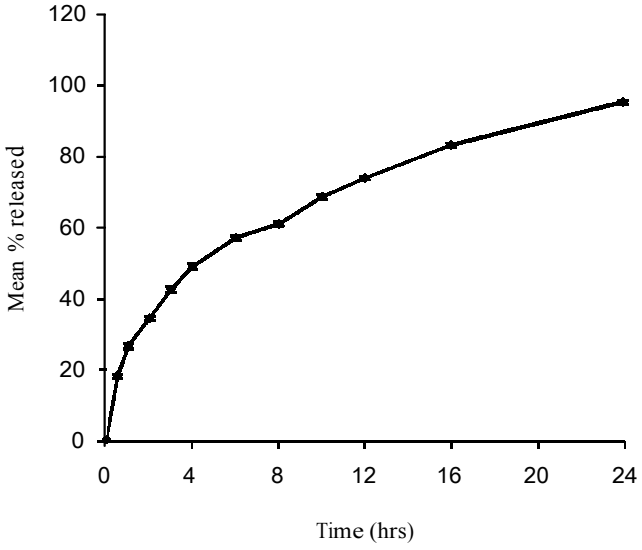


Fig 6.18: *In-vitro* dissolution profile of BCF from F2

Table 6.8: Mean ± S.D percent of BCF released from BCF floating tablets (F3)

Time(hrs)	% BCF released			Mean± SD
	1	2	3	
0	0	0	0	0
0.5	29.82	31.03	29.55	30.13±0.79
1	39.97	41.32	41.32	40.87±0.78
2	54.29	51.19	52.40	52.62±1.56
3	59.16	58.35	59.97	59.16±0.81
4	63.62	65.51	66.32	65.15±1.39
6	77.66	78.87	81.84	79.46±2.15
8	92.51	93.19	90.36	92.02±1.48
10	99.41	99.01	99.68	99.37±0.34
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16	---	---	---	---
24	---	---	---	---

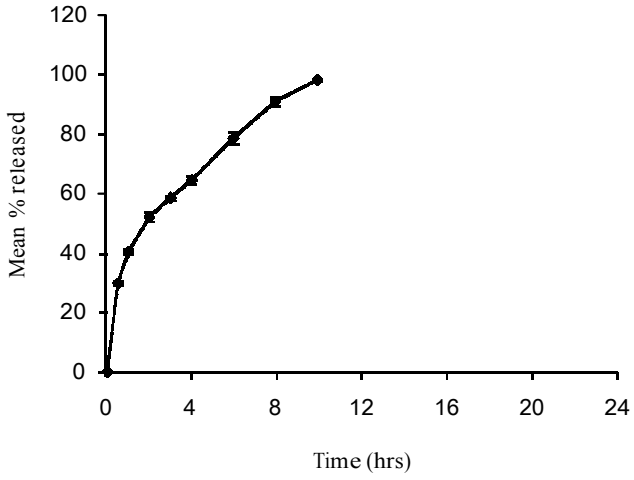

Fig 6.19: *In-vitro* dissolution profile of BCF from F3

Table 6.9: Mean ± S.D percent of BCF released from BCF floating tablets (F4)

Time(hrs)	% BCF released			Mean± SD
	1	2	3	
0	0	0	0	0
0.5	28.74	28.20	29.55	28.83±0.68
1	36.60	38.76	38.22	37.86±1.12
2	42.95	44.98	44.44	44.12±1.05
3	49.43	50.51	50.78	50.24±0.72
4	55.92	56.73	57.13	56.59±0.62
6	71.58	68.47	70.36	70.14±1.56
8	80.90	81.04	81.98	81.31±0.59
10	86.99	88.20	89.15	88.11±1.08
12	95.63	96.57	97.39	96.53±0.88
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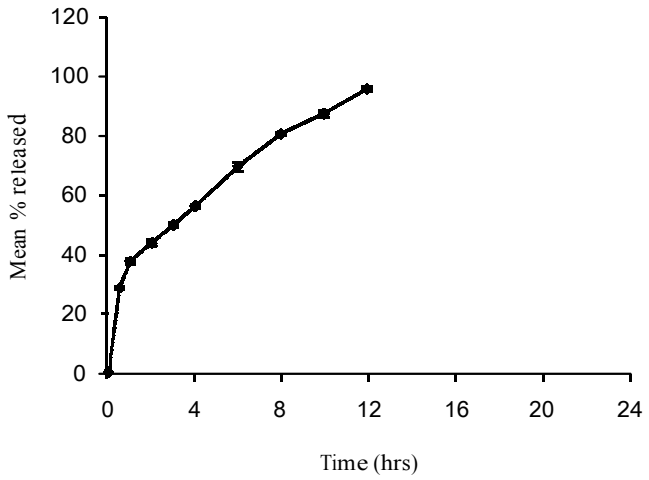


Fig 6.20: *In-vitro* dissolution profile of BCF from F4

Table 6.10: Mean ± S.D percent of BCF released from BCF floating tablets (F5)

Time(hrs)	% BCF released			Mean± SD
	1	2	3	
0	0	0	0	0
0.5	24.83	25.50	24.29	24.87±0.61
1	35.65	33.09	34.57	34.44±1.29
2	44.84	47.13	43.76	45.24±1.72
3	54.43	53.08	53.89	53.80±0.68
4	59.84	58.35	58.89	59.03±0.75
6	69.96	70.23	68.61	69.60±0.87
8	83.47	79.82	80.09	81.13±2.03
10	89.55	90.49	91.30	90.45±0.88
12	93.47	95.50	94.69	94.55±1.02
16	96.58	97.66	98.20	97.48±0.83
24	---	---	---	---

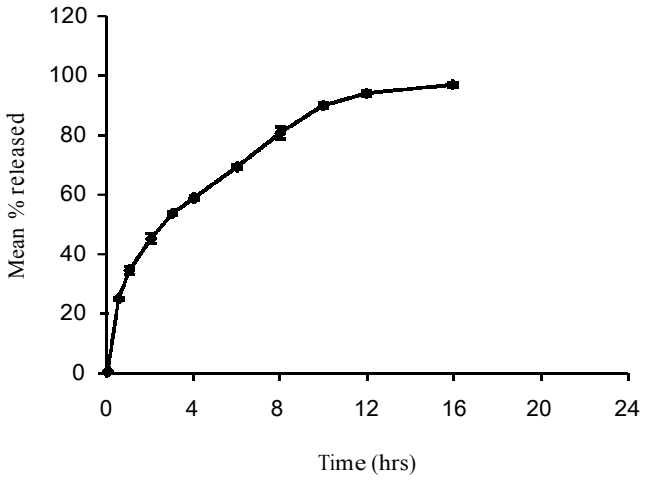


Fig 6.21: *In-vitro* dissolution profile of BCF from F5

Table 6.11: Mean ± S.D percent of BCF released from BCF floating tablets (F6)

Time(hrs)	% BCF released			Mean± SD
	1	2	3	
0	0	0	0	0
0.5	22.26	19.30	21.86	21.14±1.61
1	31.87	28.49	31.46	30.61±1.84
2	38.09	34.71	38.36	37.05±2.03
3	49.29	45.92	48.89	48.03±1.84
4	52.54	48.76	52.81	51.37±2.27
6	59.43	54.30	59.29	57.67±2.92
8	67.94	61.32	66.45	65.24±3.47
10	77.39	73.20	80.49	77.03±3.66
12	85.09	79.02	86.99	83.70±4.16
16	94.01	88.33	96.03	92.79±3.99
24	101.03	95.50	100.09	98.87±2.96

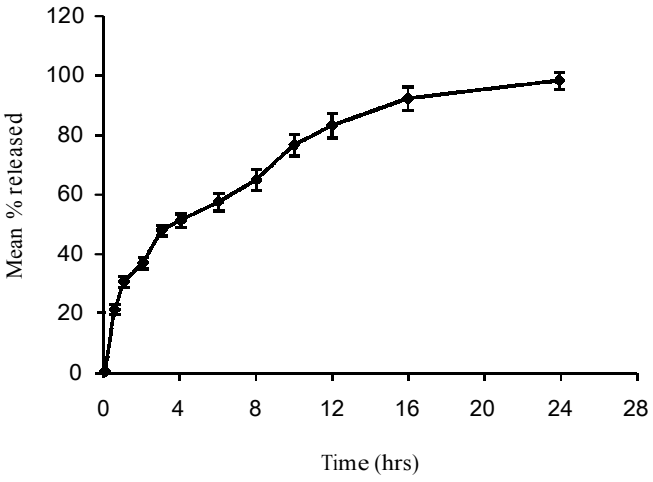


Fig 6.22: *In-vitro* dissolution profile of BCF from F6

Table 6.12: Mean ± S.D percent of BCF released from BCF floating tablets (F7)

Time(hrs)	% BCF released			Mean± SD
	1	2	3	
0	0	0	0	0
0.5	20.51	21.99	21.18	21.23±0.74
1	37.13	34.30	37.00	36.14±1.60
2	42.54	40.92	44.16	42.54±1.62
3	47.95	46.60	49.03	47.86±1.22
4	51.87	50.38	53.22	51.82±1.42
6	64.29	61.45	64.69	63.48±1.77
8	66.73	64.16	67.94	66.28±1.93
10	76.58	74.82	77.12	76.18±1.20
12	83.34	80.50	84.15	82.66±1.91
16	95.76	91.44	95.22	94.14±2.35
24	100.77	98.20	98.74	99.23±1.35

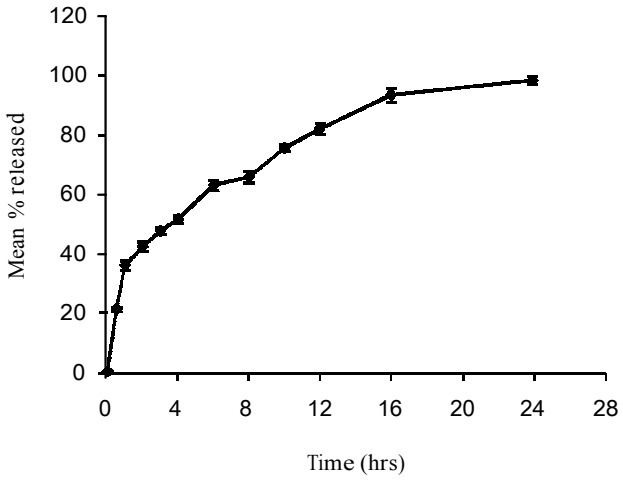


Fig 6.23: *In-vitro* dissolution profile of BCF from F7

Table 6.13: Mean ± S.D percent of BCF released from BCF floating tablets (F8)

Time(hrs)	% BCF released			Mean± SD
	1	2	3	
0	0	0	0	0
0.5	19.70	17.27	18.49	18.49±1.21
1	30.52	27.41	32.00	29.98±2.34
2	41.32	36.87	40.65	39.61±2.40
3	47.14	42.27	49.97	46.46±3.89
4	52.41	48.76	53.22	51.46±2.38
6	72.11	66.04	71.17	69.77±3.27
8	83.47	79.95	83.74	82.39±2.11
10	89.82	89.01	92.52	90.45±1.84
12	97.25	93.74	97.79	96.26±2.20
16	100.36	97.26	101.58	99.73±2.23
24	---	---	---	---

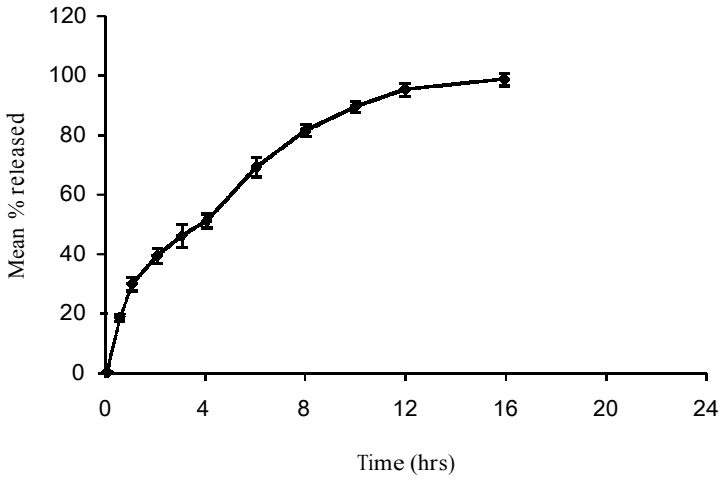


Fig 6.24: *In-vitro* dissolution profile of BCF from F8

Table 6.14: Mean ± S.D percent of BCF released from BCF floating tablets (F9)

Time(hrs)	% BCF released			Mean± SD
	1	2	3	
0	0	0	0	0
0.5	23.21	21.72	22.40	22.44±0.74
1	33.08	32.41	32.68	32.72±0.34
2	38.90	41.87	42.41	41.06±1.89
3	49.56	50.24	51.05	50.29±0.75
4	56.19	53.08	55.24	54.84±1.59
6	75.22	71.17	74.00	73.46±2.08
8	86.71	84.28	86.44	85.81±1.33
10	95.90	94.95	96.44	95.76±0.75
12	---	---	---	---
16	---	---	---	---
24	---	---	---	---

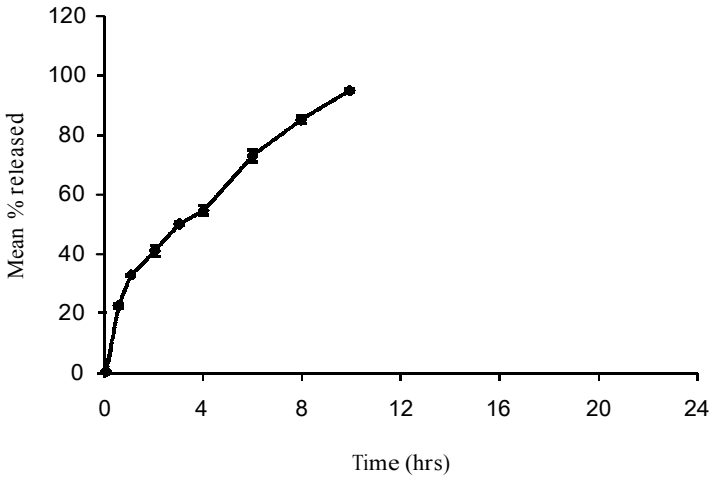


Fig 6.25: *In-vitro* dissolution profile of BCF from F9

Table 6.15: Mean ± S.D percent of BCF released from BCF floating tablets (F10)

Time(hrs)	% BCF released			Mean± SD
	1	2	3	
0	0	0	0	0
0.5	31.17	31.44	31.98	31.53±0.41
1	39.97	41.46	40.92	40.78±0.75
2	50.10	49.43	49.70	49.75±0.34
3	56.46	56.46	56.05	56.32±0.23
4	61.59	60.78	60.92	61.10±0.43
6	73.34	73.61	72.93	73.29±0.34
8	80.64	82.26	81.72	81.54±0.82
10	89.95	90.77	90.23	90.32±0.41
12	93.74	94.42	93.88	94.01±0.36
16	95.77	97.66	96.31	96.58±0.97
24	96.72	100.63	98.74	98.70±1.96

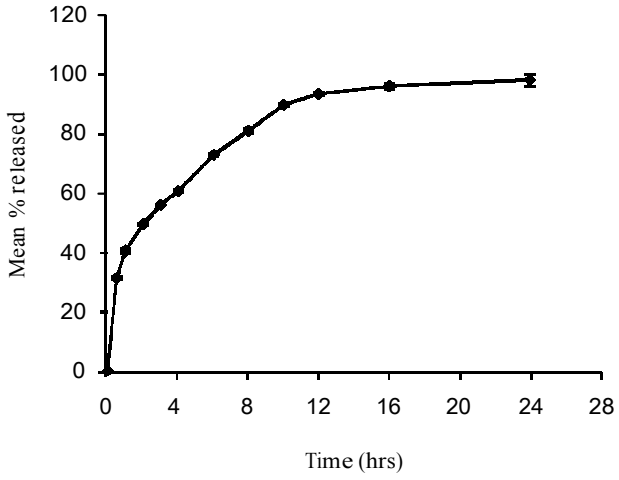


Fig 6.26: *In-vitro* dissolution profile of BCF from F10

Table 6.16: Mean ± S.D percent of BCF released from BCF floating tablets (F11)

Time(hrs)	% BCF released			Mean± SD
	1	2	3	
0	0	0	0	0
0.5	12.14	11.87	10.53	11.51±0.87
1	17.15	16.34	17.28	16.92±0.51
2	23.50	23.09	23.77	23.45±0.34
3	36.32	30.66	31.60	32.86±3.04
4	43.62	38.22	41.32	41.06±2.71
6	61.31	56.58	57.26	58.38±2.56
8	76.17	67.12	70.63	71.31±4.56
10	84.82	80.22	80.23	81.76±2.65
12	88.88	86.45	87.39	87.57±1.23
16	92.39	91.45	91.85	91.90±0.48
24	98.74	97.66	99.01	98.47±0.71

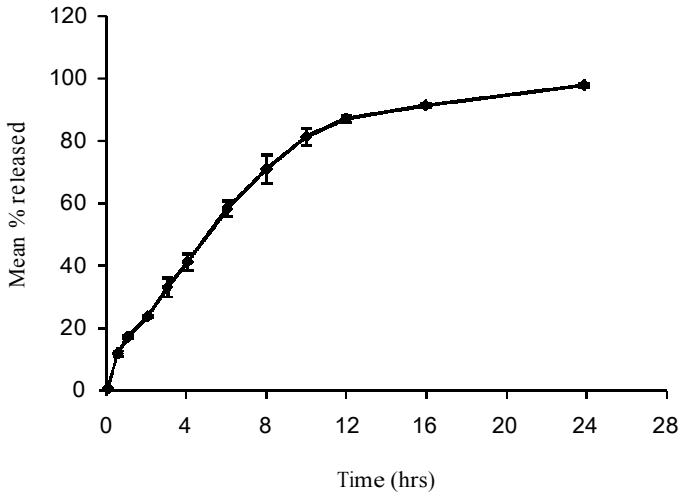


Fig 6.27: *In-vitro* dissolution profile of BCF from F11

Table 6.17: Mean ± S.D percent of BCF released from BCF floating tablets (F12)

Time(hrs)	% BCF released			Mean± SD
	1	2	3	
0	0	0	0	0
0.5	14.30	14.03	13.76	14.03±0.27
1	21.07	18.50	19.18	19.58±1.33
2	30.79	27.28	27.14	28.40±2.07
3	39.84	37.27	38.35	38.49±1.29
4	48.89	45.38	47.81	47.36±1.80
6	66.17	61.44	65.77	64.46±2.62
8	83.46	78.33	83.87	81.89±3.09
10	91.85	87.93	91.98	90.59±2.30
12	93.61	91.58	93.88	93.02±1.26
16	---	---	---	---
24	---	---	---	---

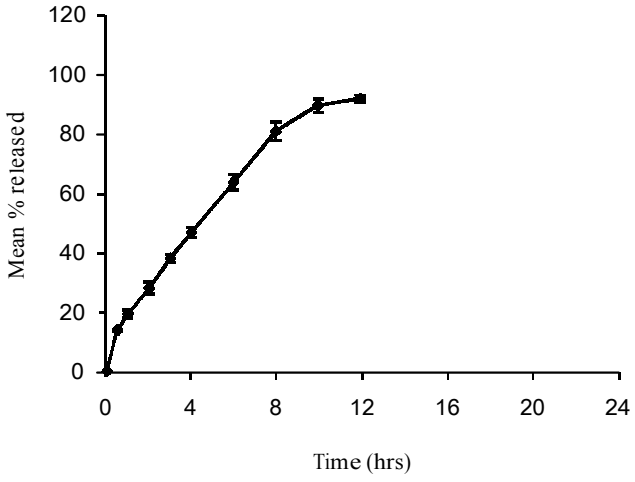


Fig 6.28: *In-vitro* dissolution profile of BCF from F12

Table 6.18: Mean ± S.D percent of BCF released from BCF floating tablets (F13)

Time(hrs)	% BCF released			Mean± SD
	1	2	3	
0	0	0	0	0
0.5	13.09	10.25	11.47	11.60±1.42
1	16.21	13.77	18.36	16.11±2.30
2	24.98	23.22	27.82	25.34±2.32
3	34.84	33.89	39.70	36.15±3.12
4	43.89	42.68	47.27	44.61±2.38
6	62.12	60.23	63.34	61.89±1.57
8	77.52	75.22	78.47	77.07±1.67
10	83.61	81.72	85.23	83.52±1.76
12	85.51	85.10	89.69	86.76±2.54
16	87.53	87.53	91.18	88.75±2.11
24	---	---	---	---

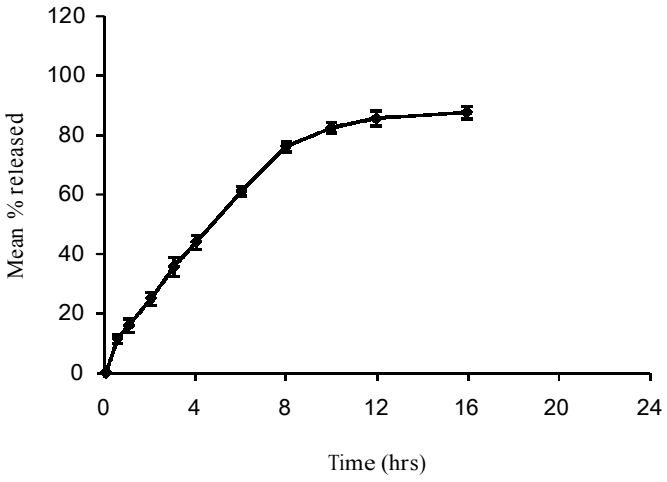


Fig 6.29: *In-vitro* dissolution profile of BCF from F13

Table 6.19: Mean ± S.D percent of BCF released from BCF floating tablets (F14)

Time(hrs)	% BCF released			Mean± SD
	1	2	3	
0	0	0	0	0
0.5	19.97	21.72	23.21	21.63±1.62
1	23.77	24.18	25.53	24.49±0.92
2	34.97	36.86	36.86	36.23±1.09
3	39.84	45.24	40.12	41.73±3.04
4	49.56	53.21	49.43	50.74±2.15
6	66.98	69.68	66.17	67.61±1.84
8	79.95	80.09	79.14	79.73±0.51
10	85.64	87.12	85.50	86.09±0.90
12	86.45	88.34	88.34	87.71±1.09
16	89.83	90.37	90.50	90.23±0.36
24	95.50	97.66	96.44	96.53±1.08

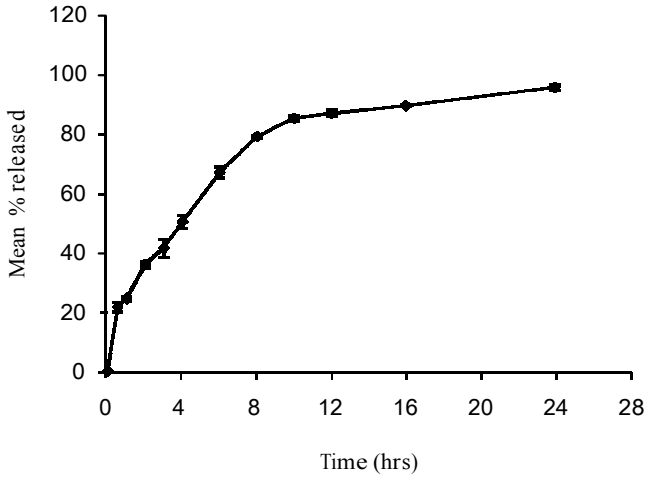


Fig 6.30: *In-vitro* dissolution profile of BCF from F14

Table 6.20: Mean ± S.D percent of BCF released from Marketed formulation (F.M)

Time(hrs)	% BCF released			Mean± SD
	1	2	3	
0	0	0	0	0
0.5	20.02	21.41	20.02	20.48±0.81
1	23.92	24.23	24.85	24.33±0.47
2	34.16	35.41	33.39	34.32±1.02
3	46.12	46.28	47.36	46.59±0.68
4	57.00	55.91	54.05	55.66±1.49
6	61.36	62.29	62.44	62.03±0.59
8	68.34	68.03	70.21	68.86±1.18
10	75.02	76.73	78.28	76.68±1.63
12	81.08	80.93	81.71	81.24±0.41
16	90.56	89.62	91.80	90.66±1.09
24	94.60	95.38	95.22	95.07±0.41

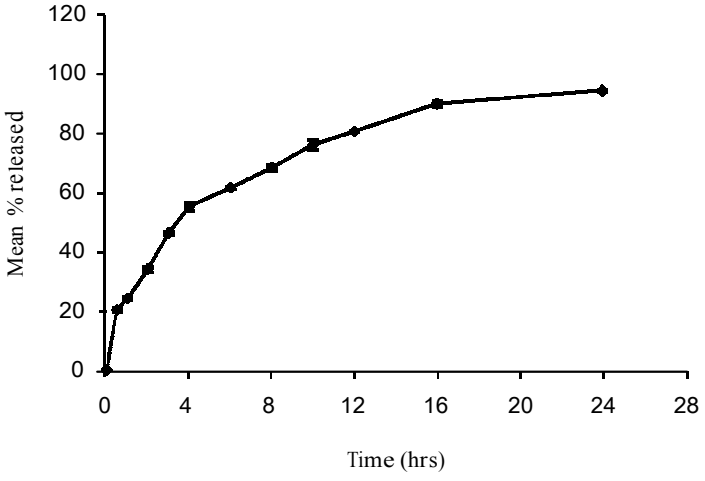


Fig 6.31: *In-vitro* dissolution profile of BCF from F.M

From the drug release data, it was evident that all the formulations gave an initial burst effect to provide the required loading dose of the drug. Also during the dissolution process, a general trend was observed in all the formulations i.e, it was observed that as the concentration of the polymer increased, there is a decrease in the drug release rate. Except formulations (F12,F13,F14), all the formulations swelled radially and axially and maintained physical integrity upto 24 hours.

In case of formulation F1, which was prepared by employing HPMC K100M (30%) as the retarding polymer and sodium bicarbonate (25%) as the effervescent agent, the drug release was sustained upto 16 hours (94.77±0.76%). In order to further extend the release upto 24 hours, the concentration of HPMC K100M was increased to 40% in formulation F2. Formulation F2 successfully sustained the drug release upto 24 hours (95.96±0.52%). Both the formulations were prepared with the same concentration of sodium bicarbonate (25%) and compressed with the hardness of 7 kg/cm^2. Both the the formulations exhibited higher floating lag times even though sodium bicarbonate was used at high concentration. This may be due to the excess hardness of the tablets. Hence, the hardness was reduced to 4 kg/cm^2 in rest of the formulations.

Formulations F3-F6 were prepared using HPMC K100M at different concentrations (20%,25%,30%,40%) and the concentration of effervescent agent was maintained constant (10%) in the formulations. Formulations F3-F6 sustained the drug release upto 10 hrs (99.37±0.34%), 12 hrs (96.53±0.88%), 16 hrs (97.48±0.83%), 24 hrs (98.87±2.96%), respectively. For the formulations F3-F6, the release rate was more sustained with increasing concentration of the polymer. The reason may be attributed to the increase in viscosity of the gel as well as the gel layer with longer diffusional path. This could cause a decrease in effective diffusion coefficient of the drug and a reduction in drug release rate. Formulation F6 successfully sustained the drug release upto 24 hours (98.87±2.96%). In order to further improve the buoyancy lag time, F7 was formulated with increased concentration of effervescent agent (12.5%), and all other excipients were same as in the formulation F6. Formulation F7 exhibited improved floating lag time and exhibited same release rate as F6. The slight increase in the concentration of sodium bicarbonate did not alter the release rate.

From the above findings, the concentration of the polymer and the effervescent agent were optimized at 40% and 12.5% respectively. The same concentration of the polymer and effervescent agent was used in rest of the formulations (F8-F14).

Further an attempt was made to study the effect of low viscosity grades of HPMC on the drug release rate. Formulations F8 and F9 containing HPMC K15M and HPMC K4M respectively sustained the drug release upto 16 hours(99.73±2.23%) and 10 hours(95.76±0.75%) respectively. From the above findings, the retarding ability of the HPMC matrices was of the order.

HPMC K100M >HPMC K15M > HPMC K4M

The rate of drug release was found to be inversely related to the viscosity grade of HPMC present in the matrix structure i.e, higher the viscosity grade slower the drug release rate from the matrix. The reason for this is higher viscosity induces greater chain entanglement than a polymer of low viscosity. Therefore, it is harder for longer chains to dissolve because of the high energy required for pulling them off the matrix. Thus, higher viscosity polymers induce the formation of a thicker gel layer after hydration. As discussed the effect of polymer viscosity was mainly due to the differences in their molecular weights.

Formulations F10 and F11 were formulated using guar gum and xanthan gum respectively. Both the formulations successfully sustained the drug release upto 24 hours. Both the formulations showed the release of 98.70±1.96% and 98.47±0.71% respectively in 24 hrs.

Formulations F12, F13 and F14 were formulated using different grades of PEO. Among the 3 formulations, F14 successfully sustained the drug release upto 24 hours. But, erosion in large extent was observed from these formulations. This may be due to the water soluble nature of PEO leading to gradual erosion of the matrix and the formulations failed to maintain the physical integrity upto 24 hours. Moreover, these formulations also failed to achieve buoyancy for the required period of time. Hence, these formulations were rejected.

The marketed formulation F.M sustained the drug release upto 24 hours and showed the release of 95.07±0.41%.

6.3. Drug release kinetics and mechanism:

The rate and mechanism of release of Baclofen from the prepared floating tablets and the marketed formulation were analyzed by fitting the dissolution data into the zero-order, first-order, Higuchi's and Korsmeyer-Peppas equation.

In case of zero order kinetics, the graph was plotted between cumulative percent of drug released versus time, and for first order release kinetics, the graph was plotted between log cumulative percent of drug remaining versus time. For Higuchi model, the graph was plotted between cumulative percent of drug released versus square root of time, and for Korsmeyer-Peppas model, the graph was plotted between log cumulative percent of drug released versus log time .The plots are shown in **Figs.6.32-6.91**.

Drug release kinetic profiles of formulation F1

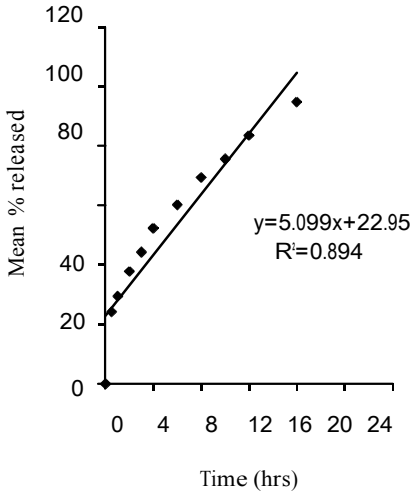


Fig 6.32: Zero order kinetic profile

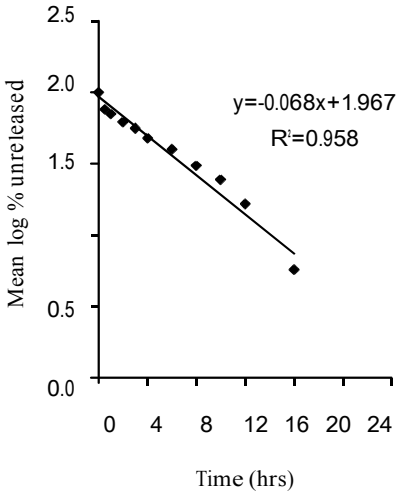


Fig 6.33: First order kinetic profile

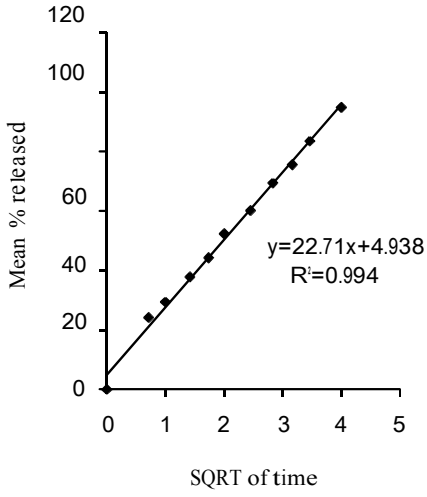


Fig 6.34: Higuchi kinetic profile

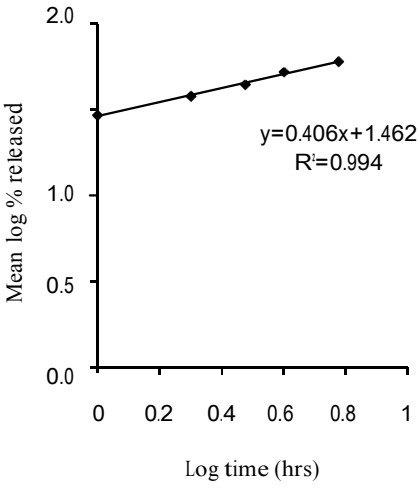


Fig 6.35: Peppas kinetic profile

Drug release kinetic profiles of formulation F2

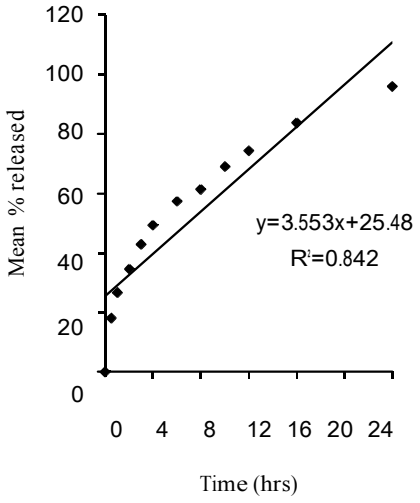


Fig 6.36: Zero order kinetic profile

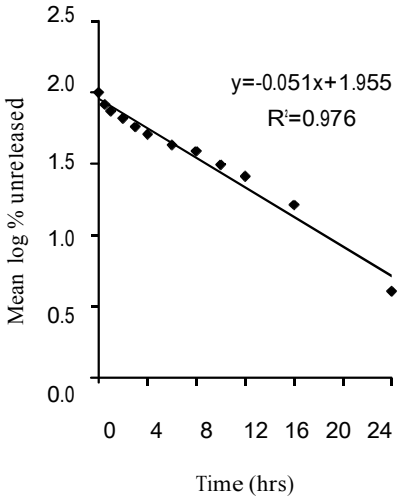


Fig 6.37: First order kinetic profile

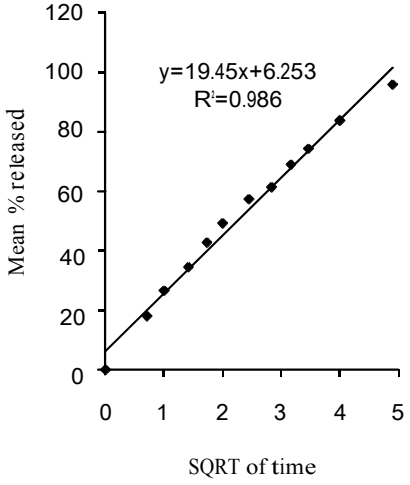


Fig 6.38: Higuchi kinetic profile

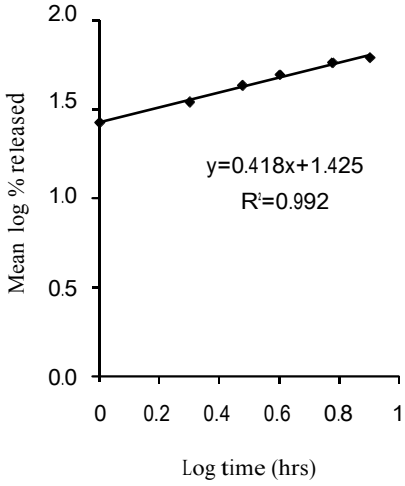


Fig 6.39: Peppas kinetic profile

Drug release kinetic profiles of formulation F3

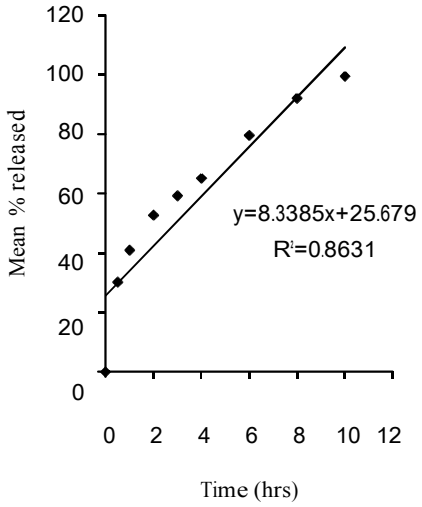


Fig 6.40: Zero order kinetic profile

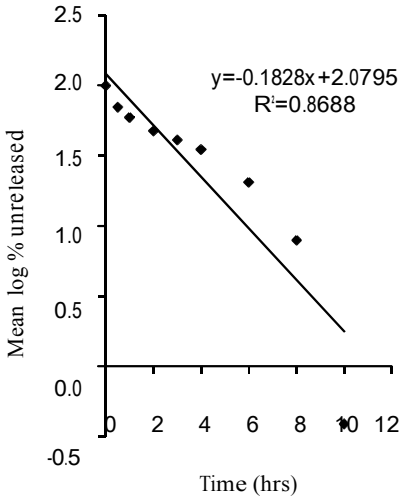


Fig 6.41: First order kinetic profile

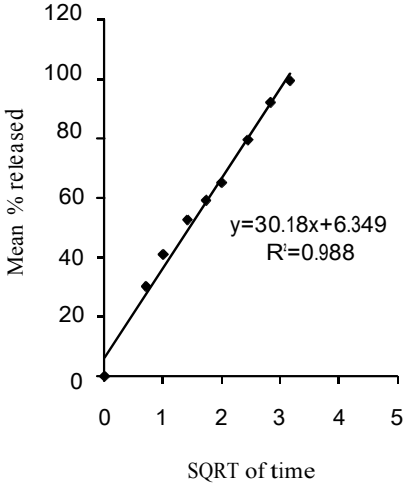


Fig 6.42: Higuchi kinetic profile

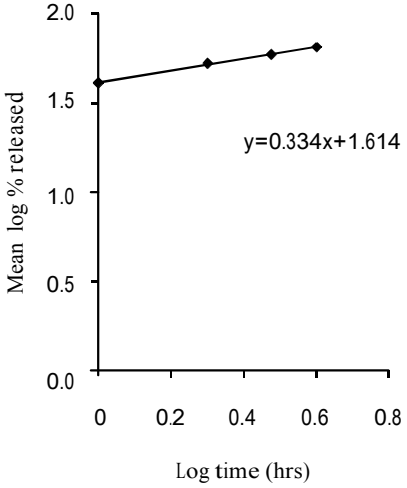


Fig 6.43: Peppas kinetic profile

Drug release kinetic profiles of formulation F4

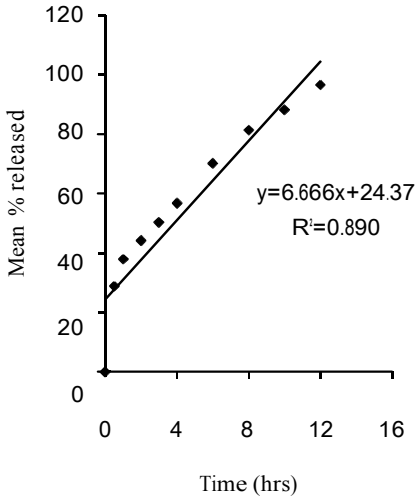


Fig 6.44: Zero order kinetic profile

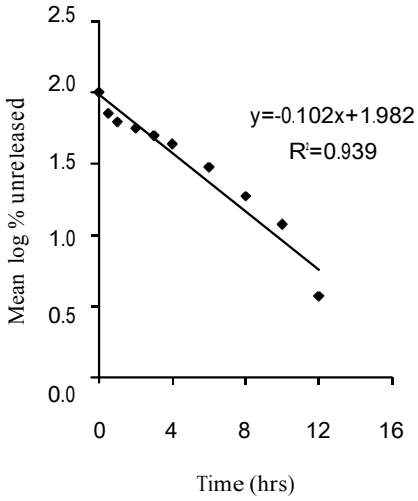


Fig 6.45: First order kinetic profile

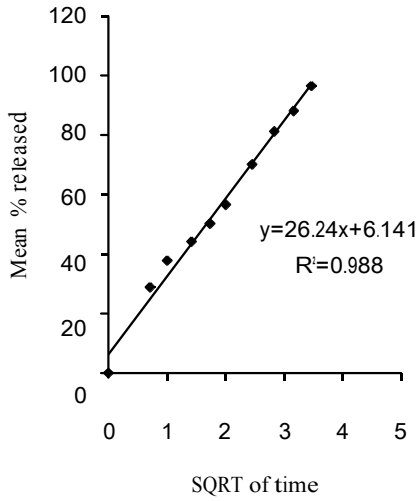


Fig 6.46: Higuchi kinetic profile

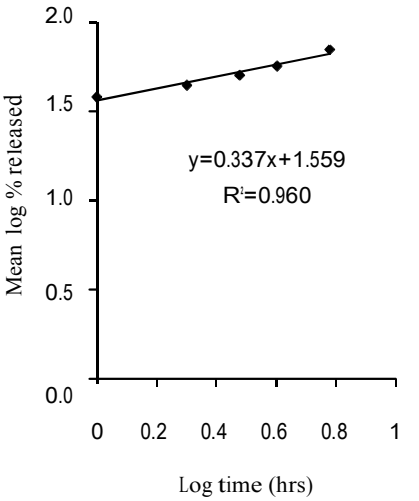


Fig 6.47: Peppas kinetic profile

Drug release kinetic profiles of formulation F5

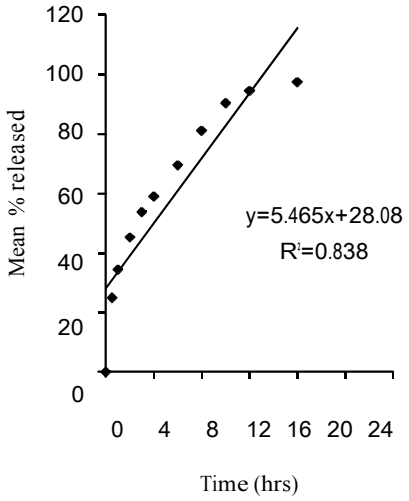


Fig 6.48: Zero order kinetic profile

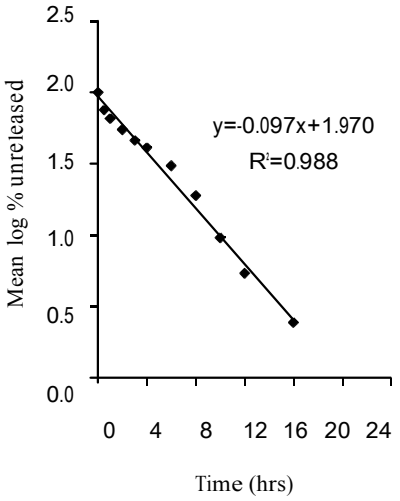


Fig 6.49: First order kinetic profile

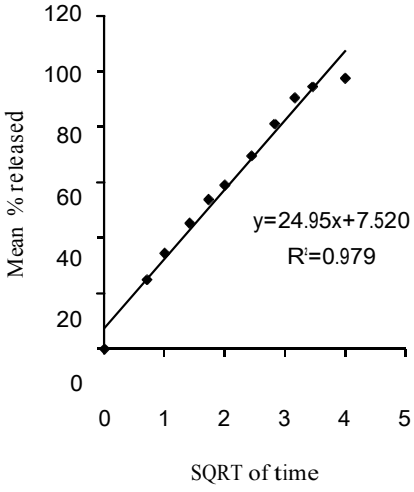


Fig 6.50: Higuchi kinetic profile

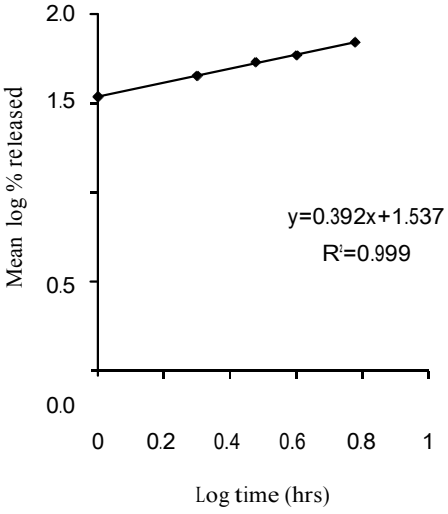


Fig 6.51: Peppas kinetic profile

Drug release kinetic profiles of formulation F6

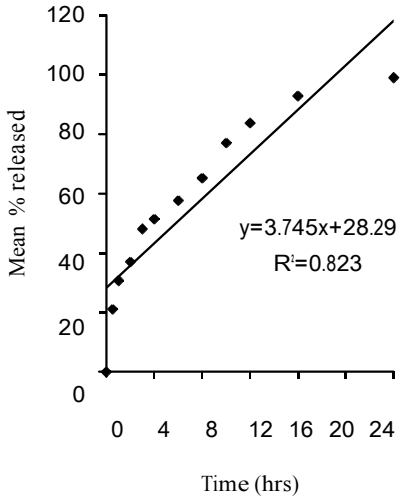


Fig 6.52: Zero order kinetic profile

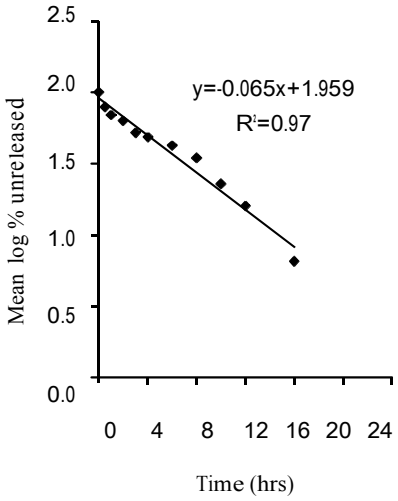


Fig 6.53: First order kinetic profile

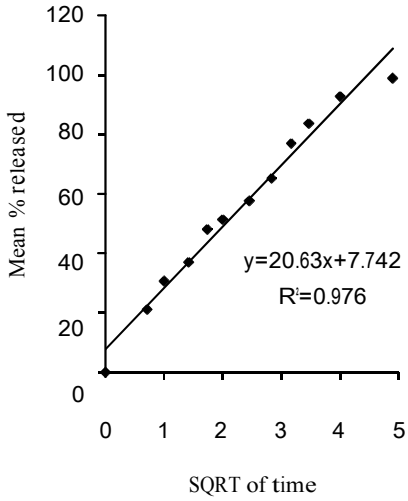


Fig 6.54: Higuchi kinetic profile

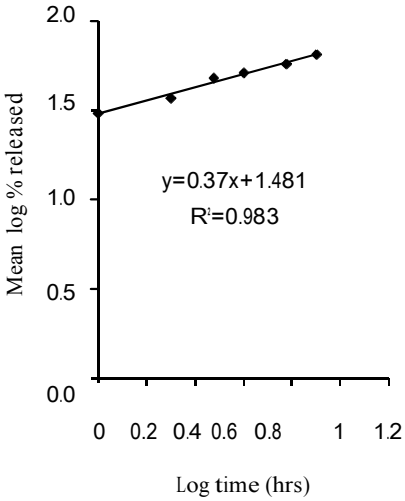


Fig 6.55: Peppas kinetic profile

Drug release kinetic profiles of formulation F7

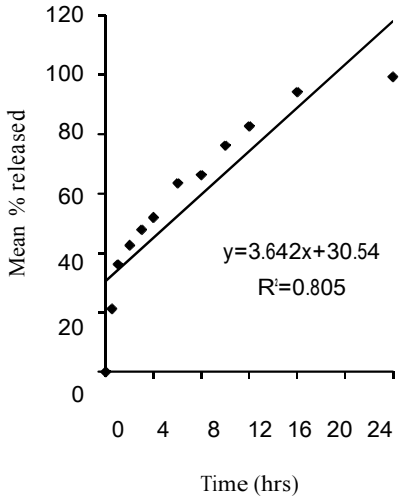


Fig 6.56: Zero order kinetic profile

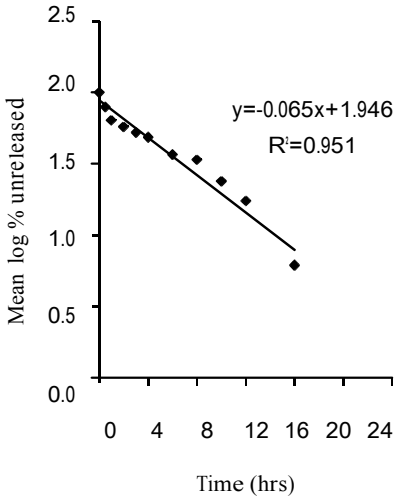


Fig 6.57: First order kinetic profile

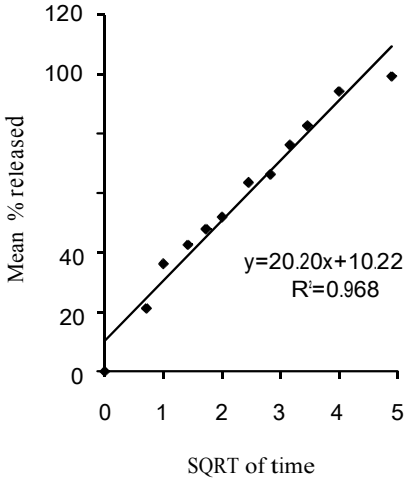


Fig 6.58: Higuchi kinetic profile

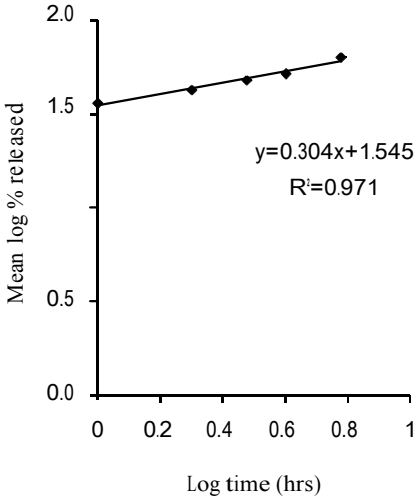


Fig 6.59: Peppas kinetic profile

Drug release kinetic profiles of formulation F8

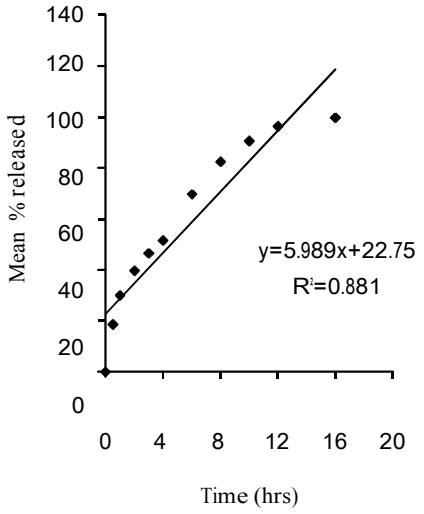


Fig 6.60: Zero order kinetic profile

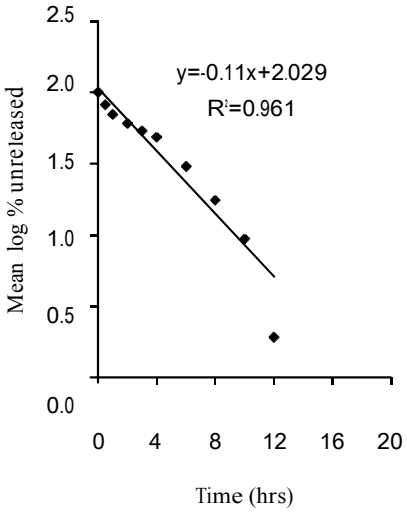


Fig 6.61: First order kinetic profile

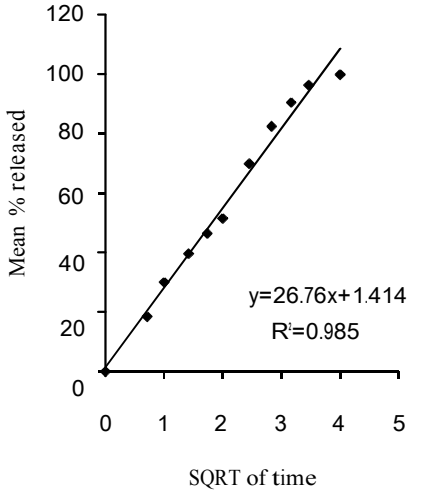


Fig 6.62: Higuchi kinetic profile

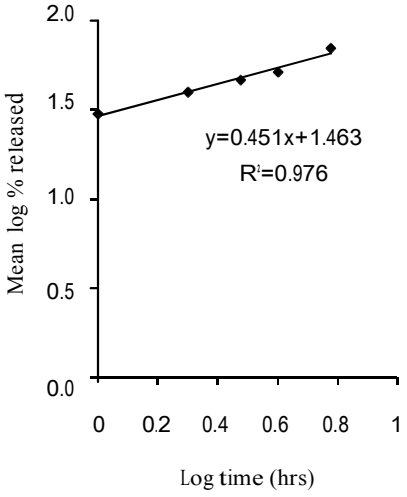


Fig 6.63: Peppas kinetic profile

Drug release kinetic profiles of formulation F9

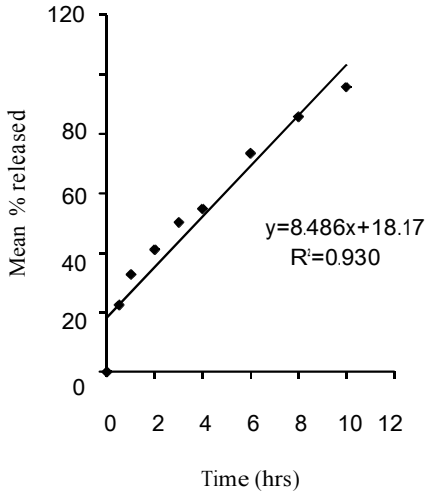


Fig 6.64: Zero order kinetic profile

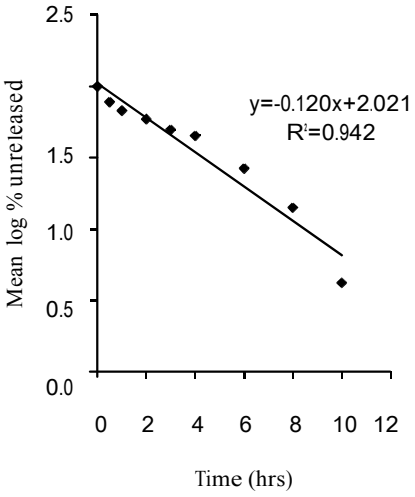


Fig 6.65: First order kinetic profile

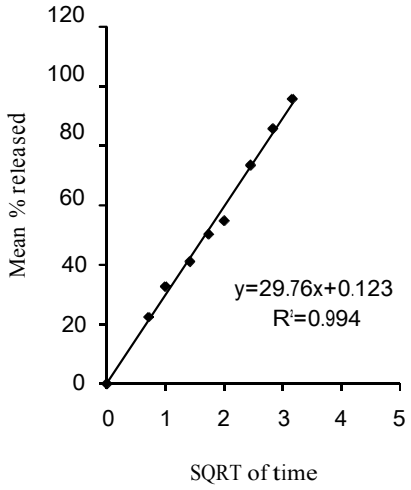


Fig 6.66: Higuchi kinetic profile

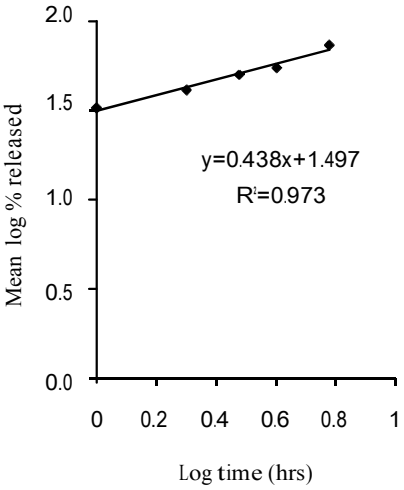


Fig 6.67: Peppas kinetic profile

Drug release kinetic profiles of formulation F10

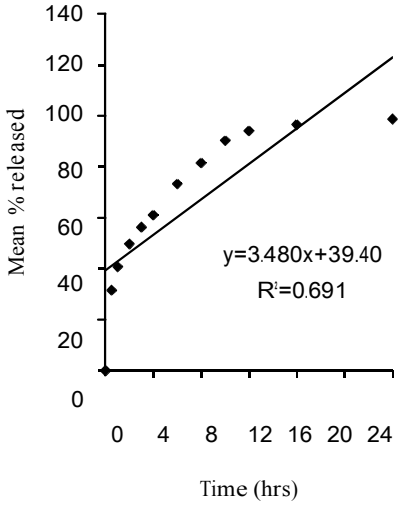


Fig 6.68: Zero order kinetic profile

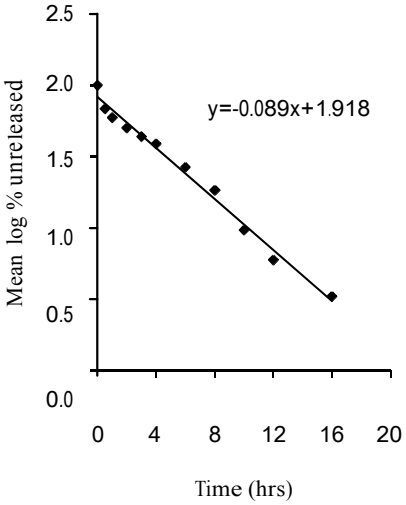


Fig 6.69: First order kinetic profile

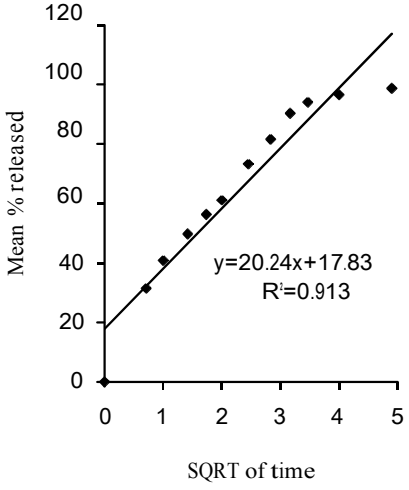


Fig 6.70: Higuchi kinetic profile

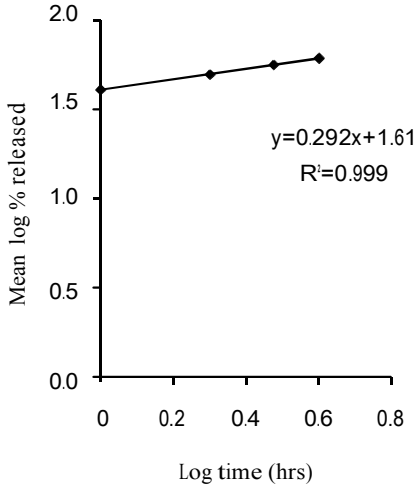


Fig 6.71: Peppas kinetic profile

Drug release kinetic profiles of formulation F11

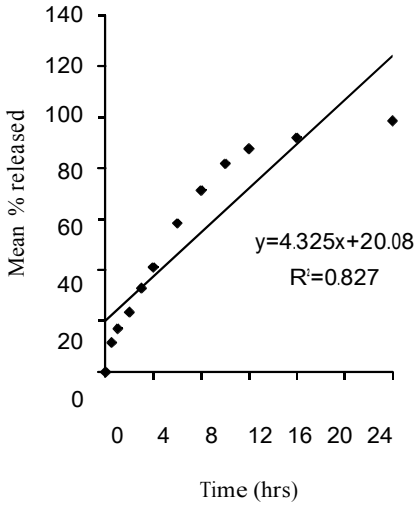


Fig 6.72: Zero order kinetic profile

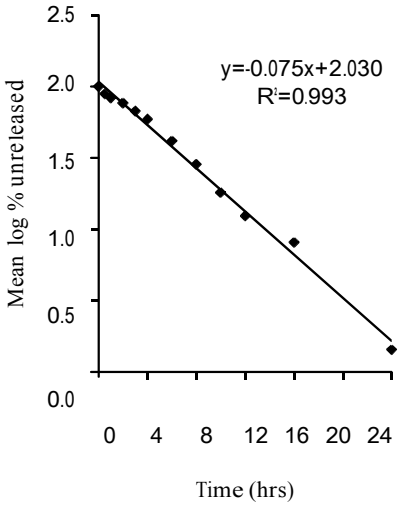


Fig 6.73: First order kinetic profile

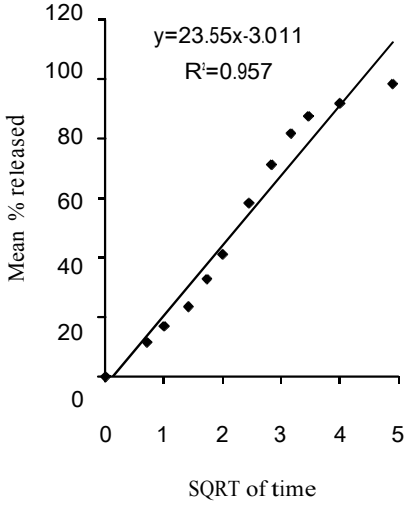


Fig 6.74: Higuchi kinetic profile

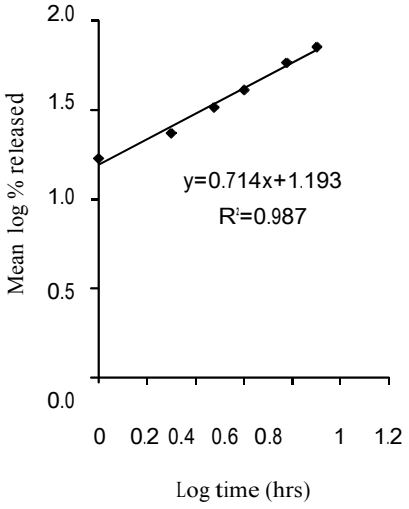


Fig 6.75: Peppas kinetic profile

Drug release kinetic profiles of formulation F12

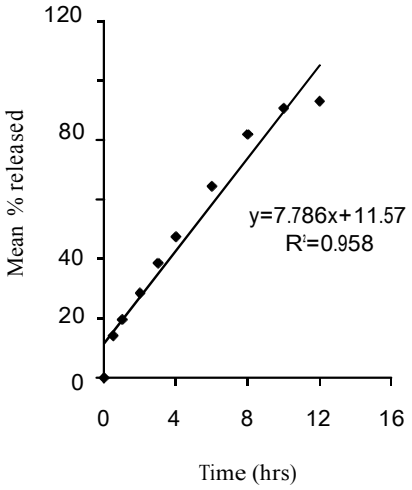


Fig 6.76: Zero order kinetic profile

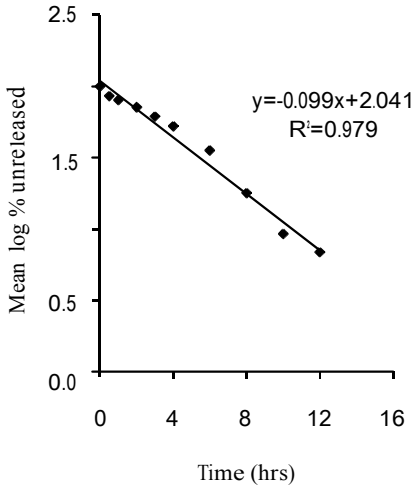


Fig 6.77: First order kinetic profile

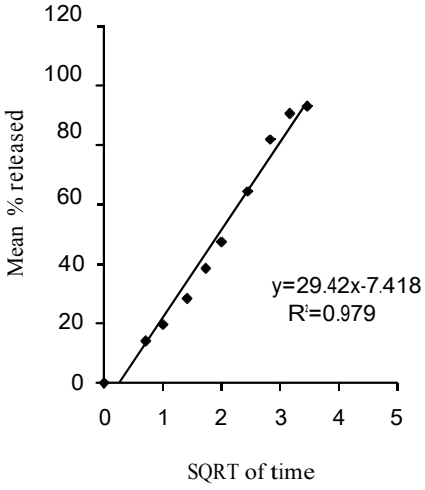


Fig 6.78: Higuchi kinetic profile

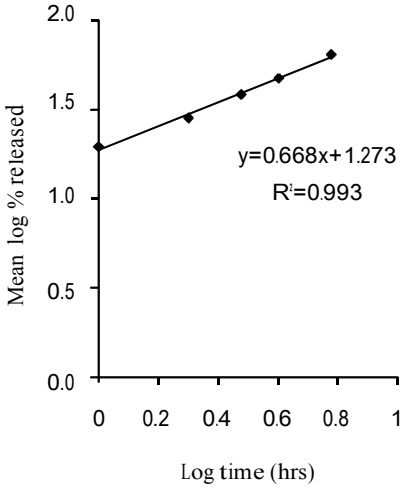


Fig 6.79: Peppas kinetic profile

Drug release kinetic profiles of formulation F13

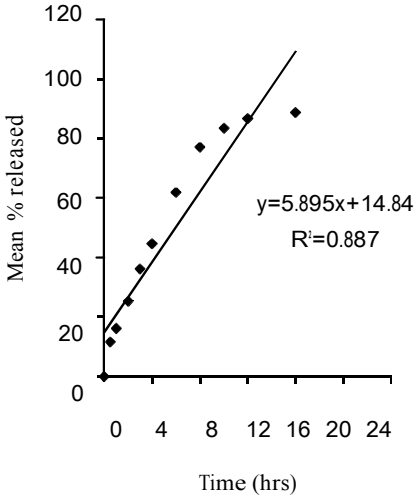


Fig 6.80: Zero order kinetic profile

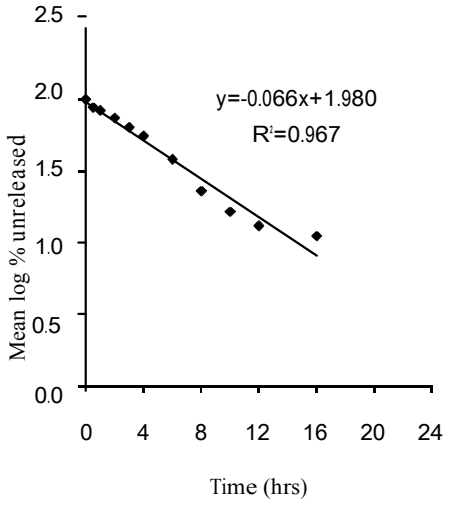


Fig 6.81: First order kinetic profile

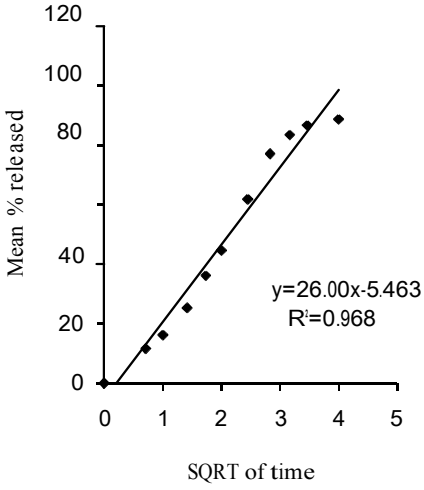


Fig 6.82: Higuchi kinetic profile

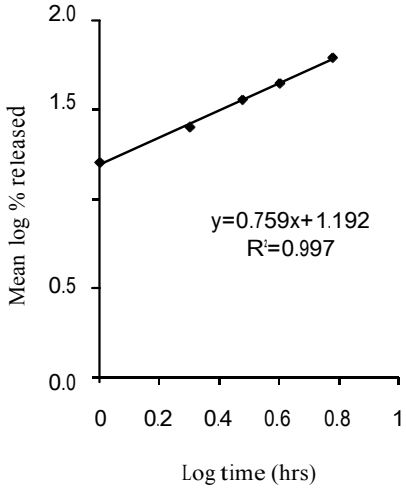


Fig 6.83: Peppas kinetic profile

Drug release kinetic profiles of formulation F14

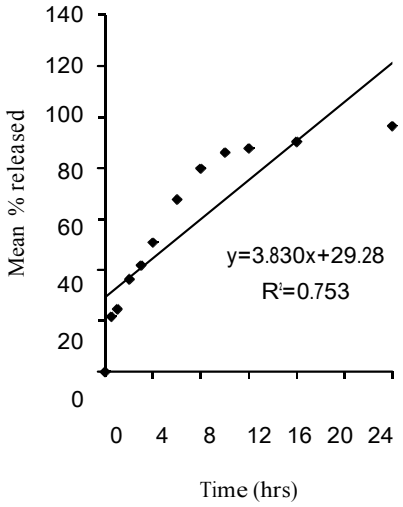


Fig 6.84: Zero order kinetic profile

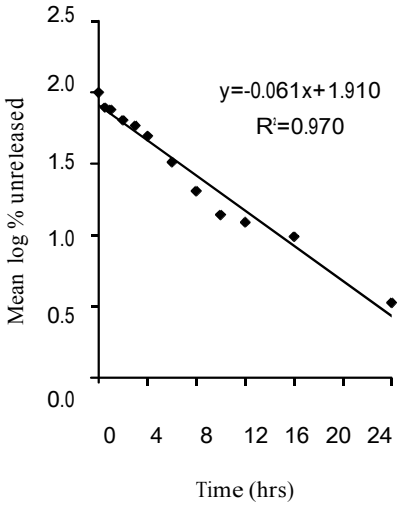


Fig 6.85: First order kinetic profile

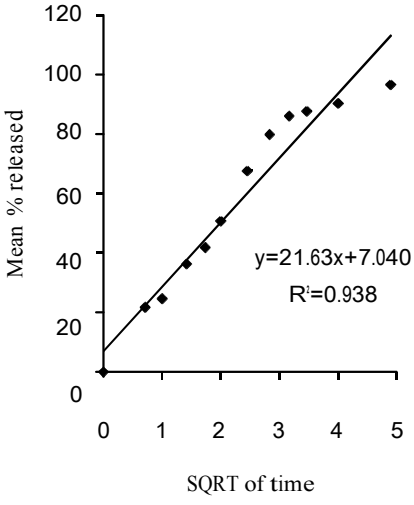


Fig 6.86: Higuchi kinetic profile

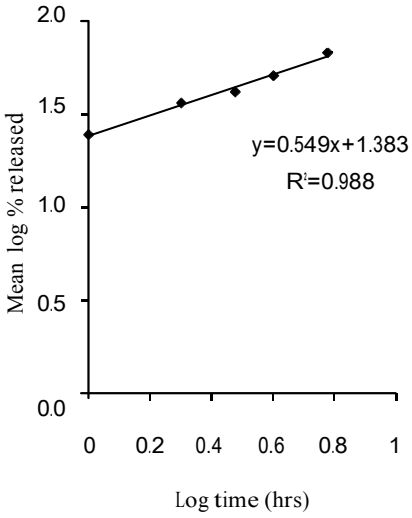


Fig 6.87: Peppas kinetic profile

Drug release kinetic profiles of Marketed formulation

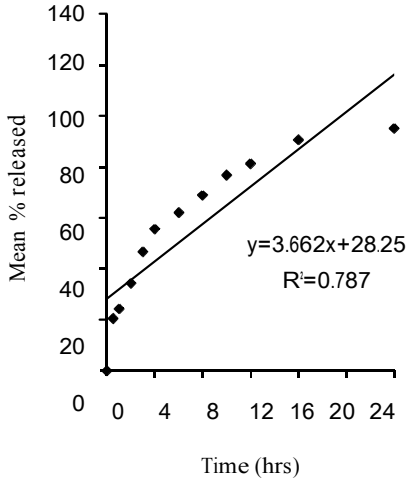


Fig 6.88: Zero order kinetic profile

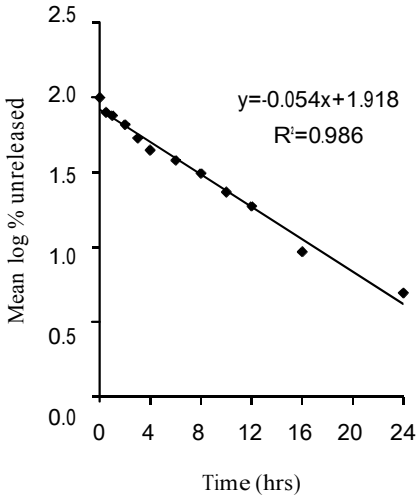


Fig 6.89: First order kinetic profile

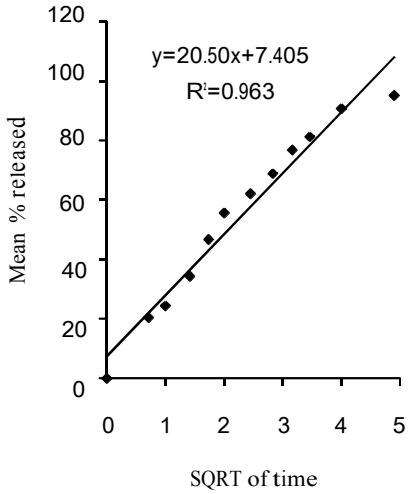


Fig 6.90: Higuchi kinetic profile

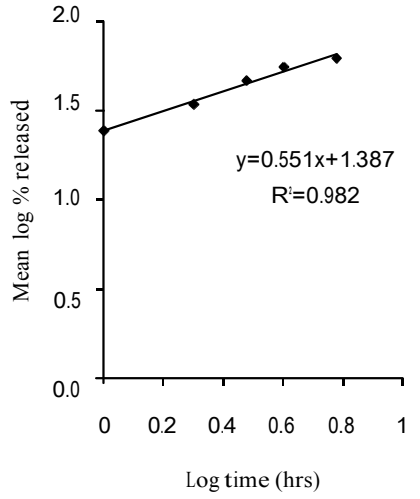


Fig 6.91: Peppas kinetic profile

The results of the regression analysis are summarized in **Table 6.21**.

Table 6.21: Release kinetic parameters for BCF SR floating formulations

Formulation	Zero order		First order		Higuchi		Peppas plot	
	R^2	K_0(mg/hr)	R^2	K(hr^{-1})	R^2	K_H(mg/$hr^{1/2}$)	R^2	n
F1	0.895	5.099	0.959	0.158	0.994	22.713	0.994	0.41
F2	0.843	3.554	0.976	0.119	0.987	19.458	0.992	0.42
F3	0.863	8.339	0.869	0.421	0.989	30.186	0.998	0.33
F4	0.890	6.667	0.940	0.235	0.988	26.246	0.961	0.34
F5	0.839	5.466	0.988	0.225	0.979	24.953	0.999	0.39
F6	0.824	3.745	0.970	0.150	0.976	20.632	0.983	0.37
F7	0.805	3.642	0.951	0.151	0.968	20.209	0.972	0.30
F8	0.881	5.989	0.961	0.253	0.986	26.762	0.977	0.45
F9	0.931	8.486	0.942	0.277	0.995	29.769	0.974	0.44
F10	0.691	3.480	0.988	0.206	0.914	20.246	0.999	0.29
F11	0.827	4.326	0.994	0.174	0.956	23.551	0.987	0.71
F12	0.958	7.786	0.979	0.228	0.980	29.428	0.993	0.67
F13	0.888	5.90	0.967	0.154	0.968	26.01	0.997	0.76
F14	0.754	3.830	0.970	0.142	0.939	21.631	0.988	0.55
F M	0.787	3.663	0.986	0.125	0.963	20.50	0.983	0.55

When the correlation coefficient 'R^2' value of zero order and first order plots were compared, it was observed that the 'R^2' values of zero order plots were in the range of 0.691 to 0.958 where as the 'R^2' values of first order plots were in the range of 0.869 - 0.994. The 'R^2' values of first order plots were found to be superior when compared to the zero order plots indicating drug release from all the formulations followed first order kinetics (drug release rate is dependent upon its concentration) suggesting the drug release in a sustained manner.

From the percent drug released versus square root of time plots, it was observed that the 'R^2' values were found to be in the range of 0.914-0.995 for the formulations studied.

The plots were linear indicating the release of drug from these formulations was governed by diffusion process.

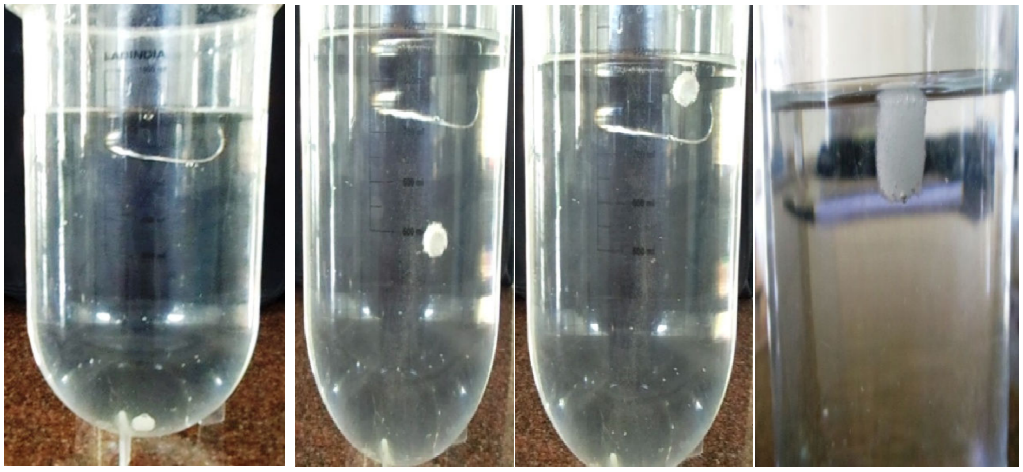
To confirm the exact mechanism of drug release from these formulations, the dissolution data was fitted to Korsmeyer-Peppas equation. For the formulations (F3-F7, F10) the release exponent 'n' was found in the range of 0.29-0.39. From the 'n' values, it was evident that the release mechanism of these formulations cannot be predicted clearly by the Power law as it appears to be a complex mechanism of swelling, diffusion and erosion.

For the formulations (F1,F2,F8,F9) the release exponent 'n' was found in the range of 0.41-0.45, indicating Fickian diffusion as the drug release mechanism.

For the formulations (F11-F14) and the marketed formulation, the release exponent 'n' was found to be in the range of 0.55-0.76 indicating non-fickian (anomalous) diffusion as the drug release mechanism from these formulations i.e, diffusion coupled with polymer relaxation.

6.4. Selection of the optimized formulation:

Based upon the buoyancy characteristics and percent cumulative drug release, the optimized formulation was selected. Formulation (F11) containing xanthan gum-40%, sodium bicarbonate-12.5% exhibited a very less floating lag time of 20.33±6.03 seconds and total floating time of 24 hours **(Fig.6.92)**. Formulation F11 released 98.47±0.71% of the drug in 24 hours. F11 showed better buoyancy characteristics and drug release profile when compared to other formulations. Hence, it was selected as the optimized formulation.



A **B** **C** **D**

A-At 0 seconds, B– At 20 seconds, C- At 23 seconds, D- After 24 hours

Fig. 6.92. Photographs taken during in-vitro buoyancy study of formula F11 in 900mL of 0.1 N HCl at different time intervals.

6.5. Comparison with the marketed product:

Optimised formulation F11 was compared with the marketed product.

Marketed product details:

BACLOF OD 20

BACLOFEN EXTENDED RELEASE (GRS) TABLETS

Manufactured by:

INTAS PHARMACEUTICALS

B.No. KL 0379

MFD.MAY 2010

EXP.APR.2012

Optimised formulation (F11) exhibited very less floating lag time of 20.33±6.03 seconds when compared to the marketed formulation (63.67±4.01 seconds). F11 showed a better drug release profile than the marketed formulation by releasing 98.47±0.71% of the drug in 24 hours. The marketed formulation released 95.07±0.41% in 24 hours. Both the formulations exhibited the total floating time of 24 hours. F11 was found to be superior

when compared to the marketed formulation. The release profiles of F11 and marketed formulation are shown in **Fig.6.93**.

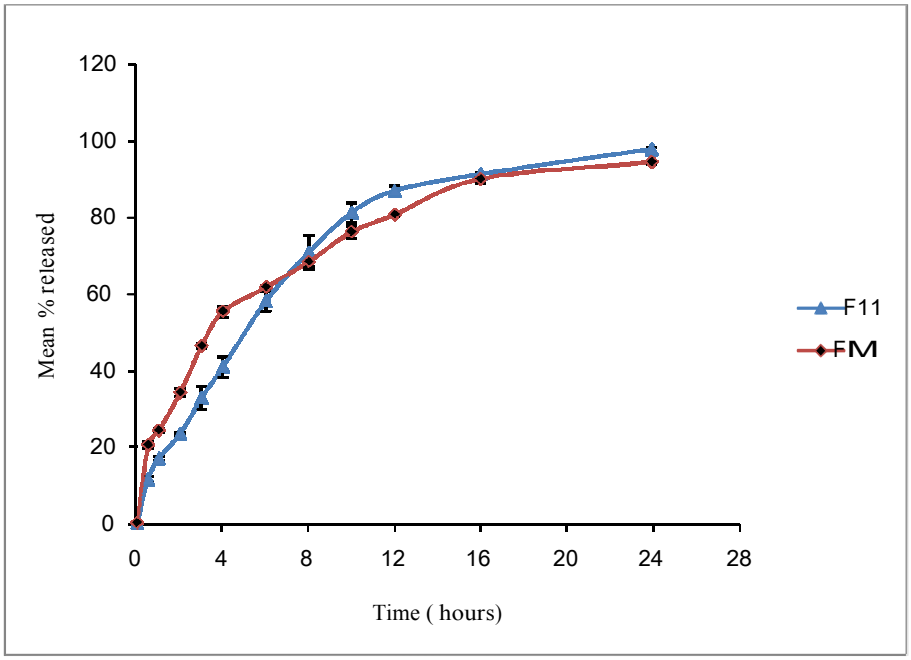


Fig.6.93. Drug release profiles of F11 and marketed formulation

6.6. Determination of Similarity factor:

Similarity factor was calculated and it was found to be 51.60. The similarity factor is within the acceptable limit (>50) which confirms the similarity between the release profiles of F11 and the marketed formulation.

CHAPTER 8

SUMMARY

AND

CONCLUSIONS

Spasticity, a condition in which certain muscles are continuously contracted, affects over 12 million worldwide. Generally, spasticity is associated with common neurological disorders like multiple sclerosis, stroke, cerebral palsy and spinal cord injury. Baclofen is the largest prescribed drug for this indication, world wide.

In the market, Baclofen is available as conventional tablets, orally disintegrating tablets and once-daily GRS tablets. Due to short elimination half-life (2.5-4 hours), the conventional and orally disintegrating tablets need to be administered 3-4 times a day (for several days)leading to poor patient compliance and there is also increased incidence of side effects with these formulations. The patient compliance can be improved and the side effects can be minimized with a once-daily sustained release formulation.

Absorption of the Baclofen is limited to stomach or upper part of the GI tract i.e, its absorption on arrival to colon (or even before) is low or nonexistent and therefore its bioavailability is incomplete when administered as a sustained release formulation. The bioavailability of the drug can be increased by making the drug completely absorbed in the stomach by gastro-retentive drug delivery system. Even though once-daily extended release GRS is available in the market (Baclof OD, INTAS pharmaceuticals), it is very expensive as it is a coated multi-layer gas generating floating tablet.

Hence, in the present investigation, efforts were made to develop once-daily sustained release gastro-retentive floating system of Baclofen which is cost effective.

The important objectives of the proposed research work are:

- Determination of solubility of BCF in 0.1N HCl.
- To develop suitable formulae and procedure for the manufacture of BCF sustained release floating tablets in a relatively economical way.
- To characterize the in-situ interactions between the drug and other excipients, if any by FT-IR examination.
- Determination of Pre-compression parameters of the powder blends of various formulations.
- To formulate BCF SR floating matrix tablets using polymers like HPMC K4M ,HPMC K15M, HPMC K100M, Polyethylene oxide WSR-301, Polyethylene oxide WSR-303 (Synthetic polymers) and Xanthan, guar gum (natural polymers) and sodium bicarbonate as the effervescent agent by direct compression technique.

- To evaluate the post compression parameters of the prepared tablets.
- In-vitro evaluation of the gastro retentive tablets for the buoyancy and release characteristics.
- To analyze the rate and mechanism of release of Baclofen from the prepared floating tablets and the marketed formulation.
- Selection of the optimized formulation.
- Comparison of the optimized formulation with the marketed product.
- Determination of similarity factor.

Solubility study:

The dissolution medium employed for the gastro-retentive tablets is 0.1N HCl (pH-1.2) (Simulated gastric fluid). Hence, the solubility of Baclofen in 0.1N HCl was determined inorder to verify whether sink condition can be maintained in the in-vitro dissolution process employing 0.1N HCl as the dissolution medium.

- Practically, the solubility of Baclofen in 0.1 N HCl (Simulated gastric fluid) was found to be 25.2 mg/mL.
- From the solubility study, it was evident that the sink condition can be maintained in the in-vitro dissolution process employing 0.1N HCl as the dissolution medium.

Drug- excipient compatibility study:

FT-IR spectroscopy was employed to ascertain the compatibility between the drug and the selected excipents.

- FT-IR spectrum of Baclofen showed the following characteristic peaks at 1093cm^{-1} (due to –C-Cl), 1526 cm^{-1} (due to -COOH), and 1626 cm^{-1} (due to –NH_2).
- These prominent peaks of drug were also present in the IR spectra of physical mixtures of drug with various excipients, thus revealing compatibility of the selected drug with the excipients.

Determination of Pre-compression parameters of the powder blends of various formulations:

The powder blends of the formulations were evaluated for micromeritic properties like bulk density, tapped density, Carr's compressibility index and Hausner's ratio.

From the results, it was evident that the powder blends of all the formulations possessed good flow properties. Hence, direct compression technique was employed for the preparation of tablets.

Evaluation of BCF floating tablets:

The prepared BCF floating tablets were evaluated for the following parameters:

Post-compression parameters: The formulated tablets were evaluated for various physico-chemical parameters like hardness, weight variation, friability, drug content uniformity.

- **Hardness:** The hardness of the formulations ranged between 4 – 7 kg/cm^2. No significant difference in hardness values of all batches of tablets prepared was observed. So, all the formulations pass the test.
- **Weight variation:** The weight variation for all the formulations was found to be within the limit (7.5% deviation).
- **Friability:** A maximum weight loss of not more than 1% of the tablet weight during the friability test is generally considered acceptable. The friability of all the tablets was within the limit (0.21%–0.80%).
- **Drug content uniformity:** From the results, the percentage of BCF in all the formulations ranged from 95.53±1.39% – 101.4±0.52%. So, all the tablet formulations were found to possess the claimed amount of the drug.

In-vitro Buoyancy study:

The study was performed using USP XXI type-II (paddle) dissolution apparatus containing 900mL of 0.1N HCl as the dissolution medium. The study was performed at the paddle rotational speed of 50 rpm and a temperature of 37±0.5°C.The floating lag time and the total floating time were recorded by visual observation using a stop watch.

- From the Buoyancy study, it was evident that hardness of the formulation greatly influences the buoyancy lag time. It was found that optimum hardness for the formulation of effervescent tablets is 4 kg/cm^2. Further increase in the hardness, drastically increased the floating lag time (F1,F2).
- It was observed that with the increase in the polymer concentration with same concentration of sodium bicarbonate in the formulations (F3-F6), the floating lag time increased gradually.

- With formulations containing the same amount of polymer of the same grade (F6,F7), floating lag time decreased with the increase in concentration of sodium bicarbonate.
- Formulations F9 and F10 containing HPMC K4M and Guar gum respectively exhibited very high floating lag times. Hence, these formulations were rejected.
- The duration of buoyancy of all the formulations (including marketed product) was found to be 24h except for the formulations (F12,F13,F14) which were formulated using different grades of PEO. The formulations also failed to maintain the physical integrity upto 24 hours. Hence, it was evident that PEO is unsuitable for the formulation of floating tablets.
- The buoyancy lag time of all the formulations (including marketed product) ranged between 14.67±1.16–584±14.42 seconds. Formulation F3 prepared using HPMC K100M-20% and sodium bicarbonate-10% exhibited very less floating lag time (14.67±1.16 seconds) and formulation F9 prepared using HPMC K4M-40% and sodium bicarbonate 12.5%, exhibited very high floating lag time (584±14.42seconds).

From the Buoyancy study, it was concluded that optimum amount of sodium bicarbonate and polymer with sufficient gel strength are essential to achieve optimum in-vitro buoyancy.

In-vitro drug release study:

In-vitro dissolution study was carried out for all the batches of matrix tablets using USP XXI type-II (paddle type) dissolution apparatus at temperature 37 $\pm$ 0.5°C and 50 rpm speed. 900 mL of 0.1N HCl was used as the dissolution medium.

- From the drug release data it was evident that, all the formulations gave an initial burst effect to provide the required loading dose of the drug.
- A general trend was observed in all the formulations i.e it was observed that as the concentration of the polymer increased, there is a decrease in the drug release rate (F3-F6).

- The rate of drug release was found to be inversely related to the viscosity grade of HPMC present in the matrix structure i.e, higher the viscosity grade slower the drug release rate from the matrix. The retarding ability of the HPMC matrices was

of the order.

HPMC K100M >HPMC K15M > HPMC K4M

- Except formulations (F12,F13,F14) all the formulations swelled radially and axially and maintained physical integrity upto 24 hours. In the formulations prepared using different grades of PEO (F12,F13,F14), erosion in large extent was observed. Moreover, these formulations also failed to achieve buoyancy for the required period of time. Hence, these formulations were rejected.
- Formulations prepared using polymers HPMC K100M (F2,F6,F7), Guar gum(F10), Xanthan gum(F11) at a concentration of 40% and effervescent agent-12.5% and the marketed formulation successfully sustained the drug release upto 24 hours and exhibited total floating time of 24 hours by maintaining the physical integrity upto 24 hours.

Drug release kinetics and mechanism:

The rate and mechanism of release of BCF from the prepared floating tablets and the marketed formulation were analyzed by fitting the dissolution data into the zero-order, first-order, Higuchi's and Korsmeyer-Peppas equation.

- The 'R^2' values of first order plots were found to be superior when compared to the zero order plots indicating drug release from all the formulations followed first order kinetics (drug release rate is dependent upon its concentration) suggesting the drug release in a sustained manner.
- The percent drug released versus square root of time plots were linear with the 'R^2' values ranged between 0.914–0.995 indicating the release of drug from these formulations was governed by diffusion process.
- To confirm the exact mechanism of drug release from these formulations, the dissolution data was fitted to Korsmeyer-Peppas equation. For the formulations (F3-F7, F10) the release exponent 'n' was found in the range of 0.29–0.39. From the 'n' values, it was evident that the release mechanism of these formulations cannot be predicted clearly by the Power law as it appears to be a complex mechanism of swelling, diffusion and erosion.
- For the formulations (F1,F2,F8,F9) the release exponent 'n' was found in the range of 0.41-0.45, indicating Fickian diffusion as the drug release mechanism. For the formulations (F11-F14) and the marketed formulation, the release

exponent 'n' was found to be in the range of 0.55-0.76 indicating non-fickian (anomalous) diffusion as the drug release mechanism from these formulations i.e, diffusion coupled with polymer relaxation.

Selection of the optimized formulation and comparison with the marketed formulation:

Formulation (F11) containing xanthan gum-40%, sodium bicarbonate-12.5% exhibited a very less floating lag time of 20.33±6.03 seconds and total floating time of 24 hours and released 98.47±0.71% of the drug in 24 hours. Hence, it was selected as the optimized formulation. Marketed formulation exhibited FLT of 63.67±4.01 seconds, TFT of 24 hours and released 95.07±0.41% drug in 24 hours. F11 was found to be superior when compared to the marketed formulation.

Determination of Similarity factor:

Similarity factor was calculated and it was found to be 51.60. The similarity factor is within the acceptable limit (>50) which confirms the similarity between the release profiles of F11 and the marketed formulation.

Conclusion: Finally, once-daily sustained release gastro-retentive floating tablets of Baclofen were successfully formulated in a relatively economical way when compared to the marketed formulation and found to be superior when compared to the marketed formulation.

CHAPTER 9

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